This is a digital copy of a book that was preserved for generations on library shelves before it was carefully scanned by Google as part of a project to make the world's books discoverable online.

It has survived long enough for the copyright to expire and the book to enter the public domain. A public domain book is one that was never subject to copyright or whose legal copyright term has expired. Whether a book is in the public domain may vary country to country. Public domain books are our gateways to the past, representing a wealth of history, culture and knowledge that's often difficult to discover.

Marks, notations and other marginalia present in the original volume will appear in this file - a reminder of this book's long journey from the publisher to a library and finally to you.

Usage guidelines

Google is proud to partner with libraries to digitize public domain materials and make them widely accessible. Public domain books belong to the public and we are merely their custodians. Nevertheless, this work is expensive, so in order to keep providing this resource, we have taken steps to prevent abuse by commercial parties, including placing technical restrictions on automated querying.

We also ask that you:

+ *Make non-commercial use of the files* We designed Google Book Search for use by individuals, and we request that you use these files for personal, non-commercial purposes.

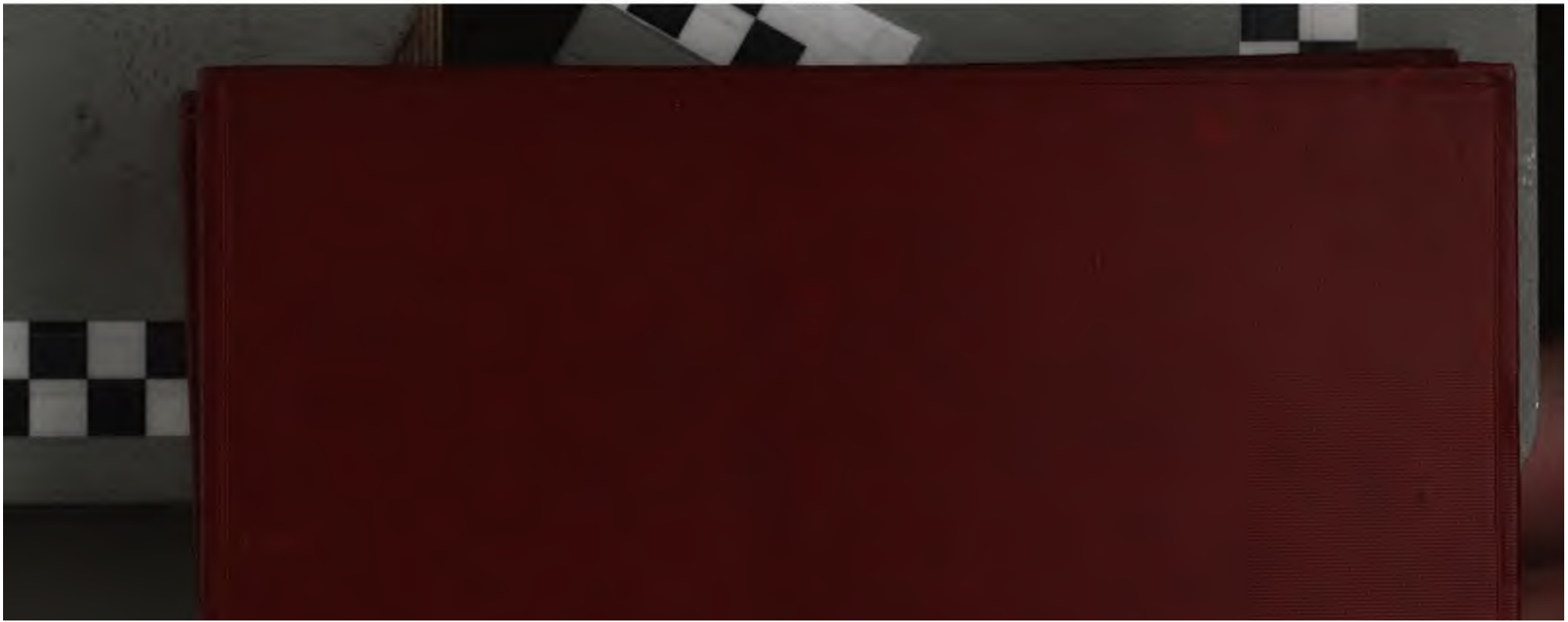
+ *Refrain from automated querying* Do not send automated queries of any sort to Google's system: If you are conducting research on machine translation, optical character recognition or other areas where access to a large amount of text is helpful, please contact us. We encourage the use of public domain materials for these purposes and may be able to help.

+ *Maintain attribution* The Google "watermark" you see on each file is essential for informing people about this project and helping them find additional materials through Google Book Search. Please do not remove it.

+ *Keep it legal* Whatever your use, remember that you are responsible for ensuring that what you are doing is legal. Do not assume that just because we believe a book is in the public domain for users in the United States, that the work is also in the public domain for users in other countries. Whether a book is still in copyright varies from country to country, and we can't offer guidance on whether any specific use of any specific book is allowed. Please do not assume that a book's appearance in Google Book Search means it can be used in any manner anywhere in the world. Copyright infringement liability can be quite severe.

About Google Book Search

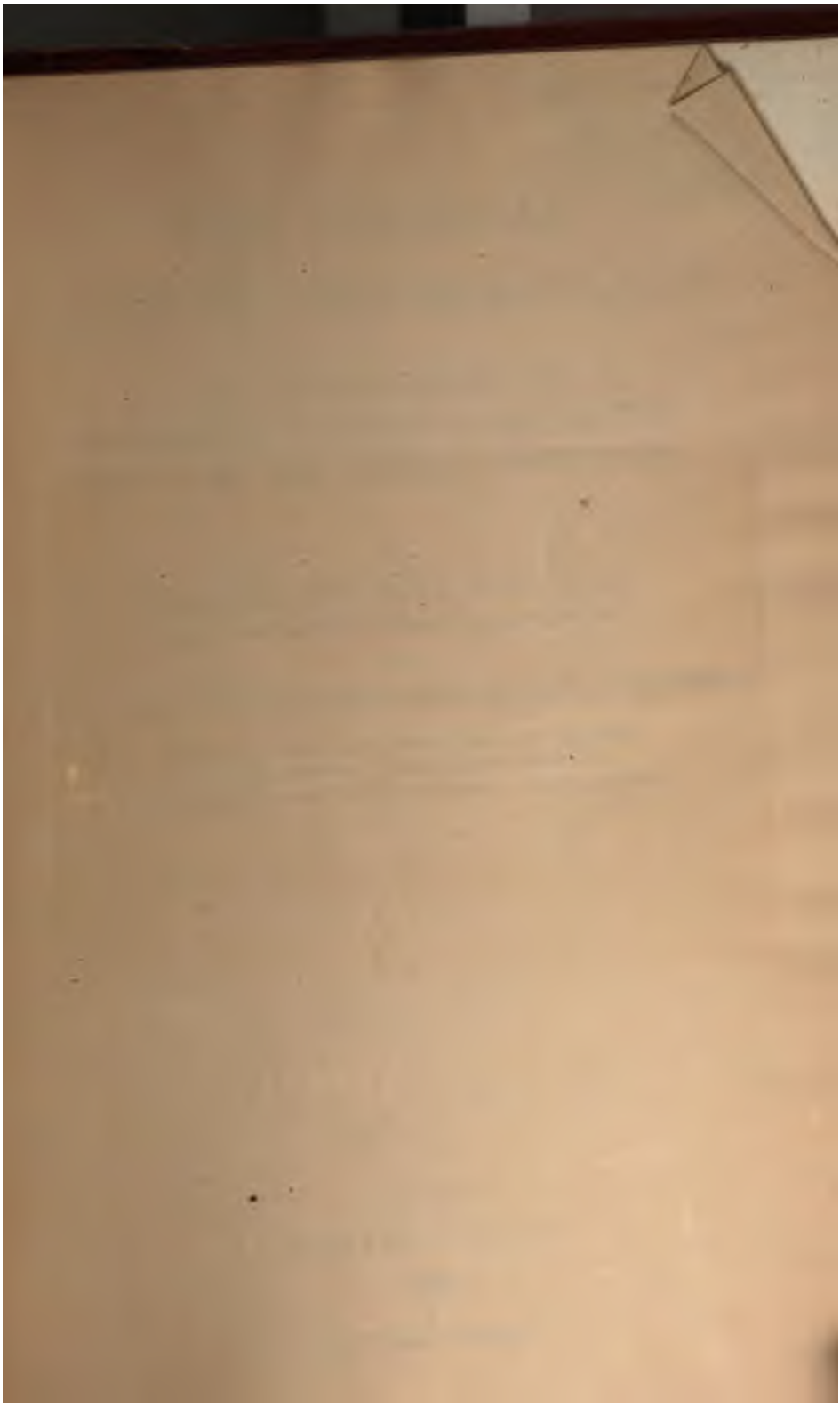
Google's mission is to organize the world's information and to make it universally accessible and useful. Google Book Search helps readers discover the world's books while helping authors and publishers reach new audiences. You can search through the full text of this book on the web at `http://books.google.com/`



LANE

MEDICAL LIBRARY

CHARLES GARDNER LATHROP FUND



THE CHEMICAL BASIS OF PHARMACOLOGY

AN INTRODUCTION TO PHARMACODYNAMICS BASED ON THE STUDY OF THE CARBON COMPOUNDS

BY

FRANCIS FRANCIS, D.Sc., Ph.D.

PROFESSOR OF CHEMISTRY, UNIVERSITY COLLEGE, BRISTOL

AND

J. M. FORTESCUE-BRICKDALE, M.A., M.D. (Oxon)

PHYSICIAN, BRISTOL ROYAL HOSPITAL FOR SICK CHILDREN
MEDICAL REGISTRAR, BRISTOL ROYAL INFIRMARY
DEMONSTRATOR OF PHYSIOLOGY, UNIVERSITY COLLEGE, BRISTOL

LONDON
EDWARD ARNOLD
1908

[*All Rights Reserved*]

LANE LIBRARY

F81
1908

'Did we know the mechanical affections of the particles of rhubarb, hemlock, opium, and a man, as a watchmaker does those of a watch, whereby it performs its operations, and of a file, which by rubbing on them will alter the figure of any of the wheels, we should be able to tell beforehand that rhubarb will purge, hemlock kill, and opium make a man sleep; as well as a watchmaker can that a little piece of paper laid on the balance will keep the watch from going till it be removed; or that, some small part of it being rubbed by a file, the machine would quite lose its motion and the watch go no more.'

LOCKE, *Human Understanding*:
Book IV, chap. iii, § 25.

40527

PREFACE

In writing the present volume the authors had no intention of adding one more to the many existing textbooks, either of Organic Chemistry or of Pharmacology. While they hope that the purport of their work has been indicated succinctly but with sufficient clearness in the title, they desire to say somewhat more by way of preface which shall serve to introduce their readers not to the subject but to the book.

Since the publication of Sir T. Lauder Brunton's Croonian Lectures, which were delivered in 1889, no book has appeared in the English language, so far as the authors are aware, dealing with the relationships between the chemical structure and physiological action of drugs; though in the Textbook of Pharmacology and Therapeutics (1901), edited by Dr. Hale White, there is a short but admirable chapter on this subject by Dr. F. Gowland Hopkins, F.R.S., of Cambridge.

It therefore seemed possible that some use might be found for a book which should lay before English readers an outline of the subject as at present understood. The book has been planned as far as possible on chemical lines, as will be seen by a reference to the headings of the chapters; occasionally, however, it has been found necessary to group together bodies which are of similar physiological action but of no close chemical relationship, as in chapters viii and xv. On the whole, however, the arrangement of the subject-matter is on lines resembling those found in works on organic chemistry, and so much of general chemical theory has been introduced as will suffice to render this portion of the subject clear to those who have not recently studied it. The authors feel, indeed, that some modifications might be introduced into the teaching of this subject to Medical Students,

which would enable them to realize its connexion with the present day Pharmacology. It is, however, in the teaching of Materia Medica that the authors would wish to see the most radical changes introduced. This subject is placed before Medical Students as if, on becoming qualified, their first duty would be to go out and gather simples on the mountain-side; whereas in actual fact, what they have to do is to gauge the relative merits or demerits of a host of synthetic remedies, the 'literature' of which is so plenteously showered upon them as soon as their names and addresses appear in the Medical Directory. The recognition of crude drugs and the tests for purity in prepared products are certainly no longer necessary knowledge for a doctor; and of the numerous preparations which the student commits wearily to memory for examination purposes, only a very small proportion are remembered and used in actual practice.

It is hoped that in some small degree the present work may point the way to reform, and that meanwhile as an introduction to a rational appreciation of one aspect of Pharmacology it may be of use both to the student, and to the practitioner who is daily brought in contact with the claims of new drugs, new preparations, and new Trade-Names. The index will, it is hoped, enable the book to be used to some extent as a work of reference, in which may be found the *prima facie* evidence for or against classes and individuals in the chemical materia medica. Though clinical experience is the only test of the value of a drug, the probable physiological action may often be fairly accurately estimated by a consideration of its chemical structure; and it seems highly probable that a large number of the synthetic remedies now on the market would never have been introduced had medical men in general been able to appreciate how little likelihood there was of their proving superior to the older preparations.

To those who are engaged solely in the study of organic chemistry, it is hoped that this volume will serve as an introduction to a particularly fascinating branch of the applied

science. The authors would feel sincerely gratified should their work contribute, even to the smallest extent, towards the encouragement of the manufacture of synthetic drugs in this country. This important industry, based as it is on the application of such general scientific principles as are discussed in the present work, is dependent for its successful development on economic and fiscal conditions; it is to be hoped that the new Excise regulations as to the use of alcohol for manufacturing purposes, and the recent alterations in the patent laws may so favourably affect these conditions in Great Britain that it may now be possible and profitable to produce synthetic drugs at home on a scale large enough to replace the imported articles.

Whenever possible, the authors have consulted the original papers dealing with the subject in hand. They would here express their indebtedness to the writings, among others, of Lauder Brunton, Fraser, Crum Brown, Cash, Dunstan, Stockman, Dixon, Marshall, Schmiedeberg, Ehrlich, Emil Fischer, Otto Fischer, Nencki, Einhorn, Loew, Hildebrandt, Hinsberg, Heinz, Knorr and Filehne, Paal, Baumann and Kast, v. Mering, Ladenberg, Sahli, Dujardin Beaumetz, and Curci. They wish particularly to acknowledge the assistance they have received from the exhaustive treatise of S. Fraenkel, whose *Arzneimittelsynthese* illustrates the entire subject with a wealth of example quite unapproached in any other volume.

Finally, they would most sincerely thank their friend and colleague, Dr. F. H. Edgeworth, Professor of Medicine at University College, Bristol, for much valuable advice and assistance during the passage of the book through the press.

F. F.
J. M. F.-B.

University College,
Bristol,
Jan. 1908.

CONTENTS

CHAPTER I

A. Chemical Introduction

PAGES

Theory of Valency, Structural formulae, Isomerism, Inertia of Carbon systems. Methods adopted for determination of constitutional formulae 1–13

B. General Physiological Introduction

Rational and Empiric methods of Therapeutics. Difficulties in correlating chemical and physiological properties. Loew's theory of poisons. General relationships between structure and action. Reactivity of the drug and the bioplasm 13–23

CHAPTER II

A. The Aliphatic and Aromatic Hydrocarbons

Their methods of preparation and properties. Methods used in the synthesis of their derivatives 24–44

B. Physiological Characteristics of the Hydrocarbons

Effect on Physiological reactivity of the introduction of Methyl or Ethyl groups, of unsaturated condition of the molecule, and of Isomeric and Stereoisomeric relationships 45–54

CHAPTER III

Changes in Organic Substances produced by Metabolic Processes

Syntheses—Sulphuric and Glycuronic acid derivatives, Compounds of Amido-acetic acid, Urea. Sulphocyanides. Introduction of Acetyl and Methyl radicals. Cystein derivatives. Processes of Oxidation and Reduction 55–80

CHAPTER IV

The Alcohols and their derivatives

The Main Group of Anaesthetics and Hypnotics

PAGES

I. General physiological action of anaesthetics and hypnotics. Overton-Meyer Theory. Traube. Moore and Roaf on Chloroform. Baglioni's theory 81–87

II. Methods of preparation and chemical and physiological properties of the Alcohols. Esters of Halogen acids, Nitrous and Nitric, Sulphurous and Sulphuric acids. The Ethers 87–104

CHAPTER V

The Alcohols and their derivatives (continued)

The Oxidation products of the Alcohols

The chemical and physiological characteristics of the Aldehydes, Ketones, Sulphones, Acids. The derivatives of the Acids. Halogen substitution products, Esters, Amides, Nitriles. Sulphur derivatives . 105–127

CHAPTER VI

Aromatic Hydroxyl derivatives

Main Group of Aromatic Antiseptics

Chemical and physiological properties of Phenols, Cresols, Di- and Tri-oxybenzenes. Recent investigations of the antiseptic power of Phenol and its derivatives, Creosote, Guaiacol, and their derivatives 128–148

CHAPTER VII

Aromatic Hydroxyl derivatives (continued)

The Hydroxy Acids

Classification of Salicylic acid derivatives. Nencki's Salol Principle. Tannic and Gallic acids 149–160

CHAPTER VIII

Antiseptic and other substances containing Iodine and Sulphur

...sification of substances introduced in place of Iodoform Iodides. Derivatives containing Sulphur—Ichthyol 161–170

CHAPTER IX

Derivatives of Ammonia

The Main Group of Synthetic Antipyretics

PAGES

Chemical and physiological character of Aliphatic and Aromatic Amines. Aniline, Acetanilide and allied substances. Classification and discussion of *para*-Amido-phenol derivatives 171–197

CHAPTER X

The Main Group of Synthetic Antipyretics (continued)

Hydrazine and its derivatives

Physiological action of Phenylhydrazine and its derivatives. The Pyrazolon group—Antipyrine, Pyramidon. General Summary of Physiological characteristics of the Ammonia derivatives . . 198–212

CHAPTER XI

I. The Group of Urethanes, Urea and Ureides

Urethane. Hedonal. Hypnotics derived from Urea. Thio-urea. Thiosinamine. Veronal hypnotics 213–220

II. The Purine Group and Pilocarpine

Diuretics and Cardiac tonics. Modification of substances of Xanthine type. Diaphoretics. Pilocarpine 221–232

CHAPTER XII

The Alkaloids

Chemical and physiological introduction. Method of classification. General principles of Alkaloidal action. The Pyridine group—Coniine, Nicotine, and allied substances 233–257

CHAPTER XIII

The Alkaloids (continued)

Pyrrolidine group—Cocaine, Atropine, Hyoscyamine. Quinoline group—Quinine, Cinchonine, and their substitutes. Strychnine and Brucine 258–283

CHAPTER XIV

The Alkaloids (continued)

PAGES

iso-quinoline group—Hydrastine, Cotarnine, Berberine. Morpholine (?)-Phenanthrene group. Morphine, Codeine, and Opium Alkaloids—Hordenine 284–303

CHAPTER XV

Synthetic Products with Physiological action similar to Cocaine, Atropine, Hydrastis

Derivatives of Piperidine, Pyrrolidine, Amido- and Oxy-amido-Benzoic acid, *para*-Amido-phenol, Guanidine, Tertiary Amyl-alcohol. Halogen and other derivatives. Substitutes for Atropine and Hydrastis 304–319

CHAPTER XVI

The Glucosides

Sinigrin, Sinalbin, Jalapin, Amygdalin, Coniferin, Phlorizin, Strophanthin, Saponarin, &c. Purgatives derived from Anthraquinone . 320–330

CHAPTER XVII

Dependence of Taste and Odour on Chemical Constitution.—Organic Dyes

I. Sternberg's views. Saccharin and its derivatives. Dulcin . 331–340

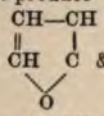
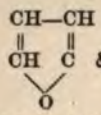
II. Odour. Physical and Chemical factors. Typical perfumes . 341–346

III. Organic dyes. Ehrlich's criticism of Loew's Theory of Poisons. Picric acid, Aurantia, Chrysoidin, Bismarck brown, Methyl violet, Methylene blue, Phosphine 347–355

APPENDIX. Curare action of Ammonium Bases, exceptions to general rule. Action of Antipyrine derivatives. Hydroberberine. Influence of Stereoisomerism on taste. Action of Rosaniline derivatives on Trypanosomes 356–358

INDEX 359–372

ERRATA

p. 4, line 3, *for* conine *read* coniine
p. 7, in formula for *iso*-butane *omit* Cl
line 18, *for* proteid *read* protein
p. 19, line 21, *for* central *read* cerebral
p. 21, line 6, *for* Kendrick *read* M^{c}Kendrick
p. 27, line 7 from bottom, *omit* double
p. 39, in first formula *for* CH_5 *read* CH_3
p. 40, line 12 from bottom, *for* synthesis *read* syntheses
p. 42, line 11, *for* alkyl *read* halogen
p. 50, line 12 from bottom (acrolein), *for* CH : CH.COH *read* CH_2 : CH.COH
p. 52, in formula for bromtoluene *for* NO_2 *read* CH_3
p. 65, line 2, *after* to *insert* produce
p. 66, in first formula *for*  &c., *read*  &c.
p. 71, line 13 from bottom, *for* $CCl_3.CH_2.CHO$ *read* $CH_3CHCl.CCl_2.CHO$
p. 75, in formula for tyrosin *for* OH_3 *read* CH_2
p. 77, formula for phenaceturic acid *should be* $C_6H_5.CH_2CO.NH.CH_2.COOH$
p. 79, line 10 from bottom, *for* $CCl_3.CH_2.CHO$ *read* $CH_3.CHCl.CCl_2CHO$
line 6 from bottom, *for* β-trichlorpropionic *read* trichlorbutyric
p. 90, in formula for ethyl nitrite *for* ONO_2 *read* ONO
p. 92, in formula for dimethyl-ethyl carbinol *for* (C_2H_3) *read* $(CH_3)_2$
p. 104, line 9 from bottom, *for* $(OC_2H_3)_2$ *read* $(OCH_3)_2$
p. 109, line 18, *for* CCl_3COH *read* $CCl_3.CH_2OH$
line 21, *for* $CCl_3.CH_2.CHO$ *read* $CH_3CHClCCl_2CHO$
p. 112, last equation but one, *for* $CaCO_3$ *read* $2CaCO_3$
p. 113, second equation, *add* $+H_2O$
p. 117, in formula for o-Xylene *for* O *read* o
p. 119, last line, *for* acid *read* acids.
p. 123, last equation but one, *for* $CH_5COOC_2H_5$ *read* $CH_3COOC_2H_5$
p. 126, line 17, *for* Ferre *read* Ferré
in last formula C_2H_5 *should in each case read* CH_3
p. 127, line 8, *for* alkyl *read* allyl
p. 131, line 2, *for* pinacol *read* guaiacol
line 9, in formula for hydroquinone *for* C_6H_5 *read* C_6H_4
p. 142, first formula, $C_6H_4.OCH_3$ *should read* $C_6H_5OCH_3$
p. 144, in formula for *p*-acetamido-benzoyl-guaiacol *for* $O.C_6H_4$ *read* $O.COC_6H_4$
p. 149, line 14 from bottom, *for* C_7H_5 *read* C_6H_5
p. 156. The second resorcin derivative contains one molecule of resorcin and two of salicylic acid and not as stated two molecules of resorcin and one of salicylic acid.

ERRATA

p. 174, sixth equation, *add* $+H_2O$ *after* CH_3NH_2

p. 181, formula for oxycarbanile *should read* $C_6H_4\langle{}^{N}_{O}\rangle COH$

p. 189, line 6 from bottom, *for* Propyl *read* Propionyl

p. 200, last line, *for* ethylene-phenylhydrazine *read* ethylene-diphenylhydrazine

p. 226, line 12, *for* Theophyllin *and* dioxypurin *read* Theophylline *and* dioxypurine
last formula, *omit* CH_3 in position *three*

p. 227, line 4 from bottom, *for* 1 : 6-dihydropurine *read* 6 dihydropurine

p. 232, line 3, *for* glyoxolin *read* glyoxalin

p. 308, in formula for triacetone-alkamine-carboxyl

for $O\langle{}^{OH}_{COOH}$ *read* $C\langle{}^{OH}_{COOH}$

p. 328, in formula for aceto-chlorhydrose *for* $(C_3H_3O)_4$ *read* $(CH_3O)_4$

THE
CHEMICAL BASIS OF PHARMACOLOGY

CHAPTER I

A. Chemical Introduction. Theory of Valency, Structural formulae, Isomerism, Inertia of carbon systems. Methods adopted for determination of constitutional formulae. B. General Physiological Introduction. Rational and empiric methods of therapeutics. Difficulties in correlating chemical and physiological properties. Loew's theory of poisons. General relationships between structure and action. Reactivity of the drug and the bioplasm.

A. CHEMICAL INTRODUCTION.

Historical.—The commencement of a general Chemical Theory was laid in 1811 by the enunciation of Avogadro's hypothesis, which stated that equal volumes of gaseous substances, under similar conditions of temperature and pressure, contain the same number of molecules: and one of the most striking results of this has been the rapid development of Organic Chemistry.

The synthesis of urea by Wöhler, in 1828, was fatal to the current theory of Vitalism, which supposed that organic substances could alone be produced through the agency of life.

The researches of Berzelius, Liebig, Wöhler, Gay Lussac, Bunsen, and others, between 1830 and 1840, showed that many atomic complexes could pass from compound to compound, behaving in a manner similar to that of the individual atom. This theory of Compound Radicals—groups of atoms which retained their existence through various chemical changes—led to the realization of the principle that in organic reactions the rupture of the molecule was always the least possible.

The investigations of Laurent, Dumas, Gerhardt and Frankland, between 1840 and 1860, led to the theory of valency, which has played so important a part in the science of Organic Chemistry.

Theory of Valency.—The outcome of the molecular hypothesis

was the possibility of assigning formulae to the following substances:

Hydrochloric acid	HCl
Water	H_2O
Ammonia	H_3N
Marsh gas	H_4C

Since experience has shown that a single atom of hydrogen never combines with more than one atom of another element, it appears that this substance possesses the faculty for combination in as low a degree as any of the known elements; a fact that is expressed in the conception that hydrogen has only one power of combining with other atoms—one valency, graphically shown by one stroke. Since oxygen combines with two atoms of hydrogen its valency is two, and for the same reason nitrogen is trivalent and carbon tetravalent.

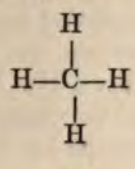
The examples given are of course the simplest that could be taken, but they clearly show the varying powers of different elements of uniting with the same substance, hydrogen.

Variation of Valency.—The question if the valency of an element is constant or not, led to a long discussion. Kekule and others regarded it as invariable as the atomic weights themselves, but the upholders of this view were drawn into many contradictions, of which the following may be taken as an example. Ammonia, NH_3, combines with hydrochloric acid to form ammonium chloride, NH_4Cl; since the valency of hydrogen and chlorine are the same, it follows that nitrogen from being trivalent in ammonia has become pentavalent in ammonium chloride. Those who regarded valency as invariable had to look upon this latter substance as a molecular compound of NH_3 and HCl, and it was represented as $NH_3 . HCl$, and but little attention was paid to the forces that kept these halves together.

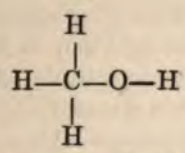
Now various organic groups may take the place of hydrogen in ammonia, it may be replaced, for instance, by the monovalent radicals methyl $(CH_3)'$ or ethyl $(C_2H_5)'$. Now in the substance triethylamine, $N(C_2H_5)_3$, nitrogen is still trivalent, and the characteristic properties of ammonia are still present; it combines with hydrochloric acid or methyl chloride, $CH_3 . Cl$, and the resulting compound $N(C_2H_5)_3CH_3Cl$ should, according to the old hypothesis of the invariability of valency, be different from the substance resulting from the addition of ethyl chloride, C_2H_5Cl, to methyldiethylamine, e.g. $(CH_3) . N . (C_2H_5)_2 . C_2H_5Cl$—but since these

two bodies are identical, it is a clear proof that the valency of nitrogen can vary, that it is three in the case of ammonia or the substituted ammonias, and five in the case of ammonium chloride or its substituted derivatives. When it is remembered that our mode of regarding valency is entirely empirical, it may be said that two valencies are latent in the former case, and that under suitable conditions these appear and are capable of binding together other atoms. In the case of carbon, the essential constituent of organic substances, the valency is taken as four, for in those compounds in which it is apparently less, such striking and characteristic properties appear, that latent valencies are presumed to be present. These cases will be discussed later.

Structural Formulae.—The direct outcome of this theory of valency was the building up of structural formulae for various compounds, relative pictures, it must be remembered, of the groupings of the atoms in the molecule. If water is represented as H—O—H, then potash is K—O—H, methane



and methylic alcohol



The somewhat empirical method by which these formulae are deduced is of the greatest importance, and one of the chief problems in organic chemistry is to determine this structural arrangement of the atoms in the molecule, and the relationship between this structure and the chemical and physical properties of the compound. Two general methods are employed, viz. the synthetic and analytical, but in the case of molecules containing few atoms, the determination of the constitution may be made on the basis of the valency of the elements concerned; this treatment is, however, necessarily limited and is only applicable, with any degree of accuracy, to molecules built up of atoms of low valency. The synthetic building up of the substance from constituents of known structural formulae, or the analytical breaking down of the body into simpler molecules, generally gives the desired data, and the results that

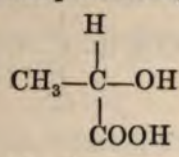
have been obtained by proceeding on such lines have amply justified the working hypothesis,—for example, the determination of the structural formulae of indigo blue and coniine, was soon followed by the synthetic formation of these substances, and in the case of the former, by its production as an article of commerce.

But the study of Organic Chemistry commences with the relatively simple investigations of the changes produced in hydrocarbons, the compounds of carbon and hydrogen, by the entrance of certain atoms or groups. Methane, CH_4, on the replacement of one hydrogen atom by chlorine gives methyl chloride, CH_3Cl, and the characteristics produced by the entrance of the chlorine atom are those that generally follow the replacement of hydrogen by that element. When one hydrogen atom in water is replaced by an organic radical such as methyl $(CH_3)'$, the simplest member of the group of alcohols is produced, $CH_3 . OH$; and again, the introduction of the hydroxyl group, $(OH)'$, into methane, causes a number of chemical, physical, and physiological differences, which are generally characteristic of the presence of that grouping.

The organic acids all contain the complex $(COOH)'$, which confers definite properties upon the hydrocarbon into which it enters. It is the knowledge of the characteristics of such groups and their combinations that is required to solve the difficult problem of determining the constitution of substances of unknown structure.

Isomerism.—But the question is further complicated by the possibility of differing arrangements of the atoms in the molecule. Supposing the hydrocarbon ethane, $CH_3—CH_3$, is considered; it is at once obvious that the hydrogen atoms are symmetrically arranged in the molecule, and that it is a matter of indifference for instance which is replaced by the hydroxyl group; that is, $OH.CH_2 . CH_3$ is clearly the same as $CH_3 . CH_2 . OH$. Theoretically, then, the theory of valency demands that only one ethyl alcohol should exist, and only one is actually known. But with the next higher hydrocarbon, propane, $CH_3 . CH_2 . CH_3$, the case is different; only the two end methyl groups, and consequently their hydrogen atoms, are symmetrical, but the hydrogen of the central CH_2 group is different; and consequently the theory of valency points to the existence of two alcohols derivable from this substance, one $OH . CH_2 . CH_2 . CH_3$, and the other $CH_3 . CH.OH.CH_3$. Now two are actually known *normal-* and *iso*-propyl alcohol, and consequently this theory gives the most satisfactory explanation of the existence of two substances of the empirical formula C_3H_8O, having the same molecular magnitude and

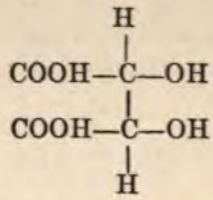
same vapour density, but different chemical and physical properties. These two bodies are said to be isomeric; they differ owing to the different arrangement of the atoms in the molecule. This theory of isomerism has played a most important part in Organic Chemistry; the existence of such isomeric bodies was realized about 1823 and the explanation followed the introduction of the theory of valency in 1860. This theory offered a most satisfactory interpretation of observed phenomena until about 1876, when evidence of its insufficiency in certain cases began to accumulate. For example, in the case of lactic acid it had been conclusively shown that its structural formula was represented by the following scheme—



and yet three isomeric modifications were known, whose chemical differences were slight, but whose physical differences were considerable. One rotated the plane of polarized light to the right, the other to the left, and the third had no action at all. Now the theory of valency could offer no explanation for the existence of such isomers, and Le Bel and van 't Hoff in 1877 brought forward the hypothesis that, were such systems considered in three dimensions a satisfactory explanation could be obtained. The central carbon was regarded as exerting its valencies in three dimensions towards the solid angles of a regular tetrahedron, and when such a configuration is investigated, it at once becomes evident that it is only when four different groups or atoms are attached to that carbon, that the existence of two forms becomes possible, one the mirrored, non-superposable image of the other. If one form rotates the plane of polarized light to the right, the other will rotate it to the left. In the case of that modification of lactic acid which has no action on polarized light, it should be possible to effect a resolution into its active components, and this was actually carried out. This theory of the Asymmetric Carbon Atom, whose four valencies are saturated by different groups or atoms, has received the fullest possible confirmation, and it may be stated that, with very few exceptions, the vast majority of carbon compounds, containing such groups, act on the plane of polarized light, and exist in three or more optically isomeric forms, depending on the number of such groups present in the molecule. Further, no case of an organic substance is known which rotates polarized

light when in solution and does not contain one or more asymmetric carbon atoms.

The example of tartaric acids is a classical illustration of the manner in which this theory has been employed, for the older theory of isomerism was incapable of explaining the existence of *dextro-* and *laevo*-rotatory tartaric, meso-tartaric and racemic acids, since it had been conclusively shown that all these forms are identical and represented by the formula

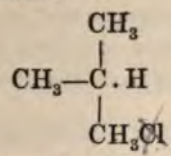


Now in this molecule there are two asymmetric carbon atoms, and it is clear that these may both rotate light to the right, in the same way as *d*-lactic acid, and the mirrored image of this would rotate light to the left. Now supposing that one rotates to the right and the other to the left, the net result is an acid, i. e. meso-tartaric acid, which has no action on light, and which is further incapable of being resolved into its active components, since it is intra-molecularly compensated. Then the acid that is synthetically obtained in the laboratory, by the employment of symmetrical forces, i. e. racemic acid, would be a mixture of equal molecules of *dextro-* and *laevo-*rotatory, and hence have no action on light, but be capable of being decomposed into its active components. Pasteur had investigated this acid in 1853 and determined the methods that could be employed for this separation; but as this line of research has, as yet, proved of but small value in the problems to be discussed, those desirous of obtaining further information on the question are referred to E. Werner, *Lehrbuch der Stereochemie*, or A. W. Stewart's *Stereochemistry* (Textbooks of Physical Chemistry edited by Sir W. Ramsay), where the vast amount of work that has been carried out on this theory, and its application to other elements, is described.

That these investigations will eventually play an important part in the preparation of physiologically active drugs is more than likely. Several of the experiments that have been made with optical isomerides will be described later, but the mere fact that *penicillium glaucum* is capable of destroying one form in preference to another,

d-lactic, for instance, compared with *l*-lactic acid, is an indication that molecules of one type have a closer connexion with the cells of that particular form of life, than the other. Still more clearly is this shown in the case of *l*-mandelic acid, which is broken down by *penicillium glaucum* and *bacterium termo*, whereas the *d*-modification is similarly decomposed by *saccharomyces ellipsoideus*. Then *d*-asparagine is sweet, whereas the *l*-modification is not.

It will be readily seen that considerations such as those just sketched further complicate the problem of determining the constitution of organic substances; as the molecular magnitude increases, so does the possible number of isomers. Butane, C_4H_{10}, is the first member of the paraffin series in which the possibility of isomerism appears, e. g. *n*-butane, $CH_3.CH_2.CH_2.CH_3$, and, trimethylmethane or *iso*-butane



But when the hydrocarbon $C_{13}H_{28}$ is considered, the possible number is 802, and the difficulties of assigning constitutional formulae to complex substances becomes at once apparent. Take for example the proteid group; their molecular magnitude, compared with the majority of organic substances, is enormous—it is, perhaps, questionable whether it is accurately known for any single member. Their decomposition products are numerous, and certainly many of these are simple, yet the rupture of the molecule has been so deep, that we are, up to the present, incapable of piecing them together, and in consequence are in ignorance of the structure of the original substance. But E. Fischer's method of dealing with this problem, by the syntheses of the so-called polypeptides, makes it appear quite likely that this extremely important question may be eventually solved. As far as can be seen at present, there appears to be no limit to the possible number of combinations and permutations among the relatively few elements found in organic substances; this is to be traced firstly to the fact that carbon possesses the peculiar property of forming, with other carbon atoms, open and closed rings. This tendency to self-combination is much more marked in the case of carbon, than in that of any other element: not only are molecules known containing up to 30 carbon atoms linked to each other,

but this accumulation does not cause the slightest indication of instability. And the other cause operating is the resistance towards disruption, due to the peculiar property carbon confers on molecules into which it enters. Although nitro-glycerine, for instance, breaks up with a large evolution of heat, showing that strong forces are tending to decompose it, yet within fairly wide limits it is a strikingly stable substance. It is due to this property, often alluded to as the inertia of the carbon system, that isomerism is observable among carbon compounds to a very much greater degree than in the case of any of the other elements, for it implies the continued existence of the less stable form—Organic Chemistry and not Inorganic is the region of isomerism. It is further in consequence of this inertia, that Organic Chemistry is the region of slow reactions and consequently of measurements of velocity; and from it follows the important principle that in determining the constitution of an organic substance the least possible number of carbon linkages are broken in any reaction that it undergoes.

Determination of Constitutional formulae.

Before it is possible to fully investigate any organic substance it is necessary either to obtain it pure or to be able to purify one or more of its derivatives. The usual criterion of purity in the case of a solid is constancy and sharpness of melting-point on recrystallization from different solvents, and although this is not invariable, the exceptions are but rarely met with. The effects of even minute traces of impurity on the melting-point are occasionally very great, and may be compared with the differing physiological reactions of, say, natural and artificial salicylic acid, which only differ by the presence of minute traces of impurity in the latter preparation. In this connexion it may be mentioned that the great power of crystallizability of so many of the solid aromatic substances has played a very considerable part in the investigation of bodies belonging to that class.

In the case of liquids, constancy of boiling-point is the most important criterion; but again, constant boiling mixtures are not uncommon, and if this be suspected, the best method is, if possible, to convert the liquid into a solid derivative, and carry out the investigations upon this.

Although these standards of purity are by no means all that are at the disposal of the Organic chemist, they are the most important and most generally adopted.

But the methods available for obtaining this purity are limited, and there are large groups of substances which up to the present have resisted all attempts at investigation, owing to the impossibility of either purifying them or converting them into crystallizable derivatives.

It will be clear, from what has been previously stated, that the first factors necessary for the elucidation of the constitutional formula will be the quantitative composition and molecular weight of the substance in question. It is not proposed to describe in detail the methods employed for the determination of either of these constants; the data for the first are obtained by the complete oxidation of a known weight of the substance to its final oxidation products, water and carbon dioxide, the amount of the former being determined by absorption by a known weight of calcium chloride; of the latter by absorption in caustic potash solution, and from the results of this combustion the percentage amounts of carbon and hydrogen are calculated. If nitrogen is present, the operation is carried out in an atmosphere of carbon dioxide, and under these conditions free nitrogen is evolved and its volume measured. Oxygen is always determined by difference, and other elements are estimated by special methods, of which a full account is to be found in any of the textbooks on Organic Chemistry. From the percentage composition the least ratio of the atoms present is readily calculated and the empirical formula obtained. This may represent the true molecular weight, or the latter may be a simple multiple of it. This magnitude may be determined from a knowledge of the density, based on Avogadro's hypothesis, or by the determination of the lowering of the freezing-point or raising of the boiling-point of a pure solvent,—the latter methods possessing great importance in the case of those substances which cannot be volatilized without decomposition. The molecular weight may also be determined, with a high degree of probability, from purely chemical considerations, and the identity of the constants obtained by both methods is of the greatest value to the molecular hypothesis.

Two cases will now be taken as illustrations of what has been previously stated.

I. On analysis, acetic acid gives the following results:—

$$\begin{aligned} C &= 40{\cdot}0\,\% \\ H &= 6{\cdot}6\,\% \\ O &= 53{\cdot}3\,\% \end{aligned}$$

The simplest ratio of the atoms present is then:

$$C = \frac{40{\cdot}0}{12} = 3{\cdot}3$$

$$H = \frac{6{\cdot}6}{1} = 6{\cdot}6 \qquad \text{or } [CH_2O]$$

$$O = \frac{53{\cdot}3}{16} = 3{\cdot}3$$

The empirical formula for this substance is consequently CH_2O, but since the density is 30, the molecular weight is 60, and therefore the molecular formula is $[CH_2O]_2$ or $C_2H_4O_2$. This same formula can be arrived at by purely chemical considerations such as, for instance, the action of phosphorus pentachloride, which results in the formation of a substance of the formula C_2H_3OCl. Since one of the general reactions of this reagent is to replace the hydroxyl group (OH) by chlorine, the deduction follows that the simplest formula for acetic acid must be $C_2H_3O.OH$. The question then arises as to the manner in which the atoms are grouped in this molecule; the action of phosphorus pentachloride has shown the presence of an hydroxyl group (OH), and this is also borne out by the formation of a series of salts in which the hydrogen of this grouping is replaced; for instance, silver acetate, $C_2H_3O.OAg$. The next problem is the nature of the atomic arrangement of the residue $[C_2H_3O]'$, when the following line of argument may be employed. The acid chloride, acted upon by ammonia, gives hydrochloric acid and an amide, a reaction represented by the equation:

$$[C_2H_3O]'Cl + NH_3 = HCl + [C_2H_3O]'NH_2.$$

The amide thus obtained can be dehydrated by means of phosphorus pentoxide, and a substance of the empirical and molecular formula C_2H_3N results:

$$[C_2H_3O]'NH_2 - H_2O = C_2H_3N.$$

The resulting derivative is methyl nitrile and may be synthesized by the action of potassium cyanide on methyl iodide

$$CH_3I + KCN = KI + CH_3CN.$$

Since but one molecular structure is possible for methyl iodide, it follows that C_2H_3N also contains this methyl group, which was present throughout the series of reactions and consequently in acetic acid itself. Moreover, methyl nitrile, warmed with dilute acids, passes back, by the absorption of water, into acetic acid.

The presence of two groupings (CH_3) and (OH) in the acid have now been proved, and since the synthetic formation of methyl nitrile indicates that the second carbon atom is directly attached to the first, the constitutional formula for acetic acid is

$$CH_3 . C\begin{matrix}O\\OH\end{matrix}$$

[By the replacement of the OH group by chlorine, the reactive acid chloride results:

$$CH_3 . C\begin{matrix}O\\Cl\end{matrix}$$

The amide has the formula

$$CH_3 . C\begin{matrix}O\\NH_2\end{matrix}$$

and the process of dehydration is indicated by the dotted line. The reabsorption of water by the nitrile, $CH_3 . CN + H_2O =$

$$CH_3 . C\begin{matrix}O\\NH_2\end{matrix}$$

and this $+ H_2O =$

$$CH_3 . C\begin{matrix}O\\ONH_4\end{matrix}$$

Ammonium acetate.]

It may be further noted that all the reactions described point to the molecular formula of the acid as $C_2H_4O_2$ and not CH_2O.

II. The analysis of benzene gave the following data:

$$C = 92{\cdot}3\,\%$$
$$H = 7{\cdot}7\,\%$$

the simplest ratio of atoms present is

$$C = \frac{92{\cdot}3}{12} = 7{\cdot}7$$
$$H = \frac{7{\cdot}7}{1} = 7{\cdot}7 \quad \text{or [CH]}$$

The empirical formula is therefore CH, but since the density is 39 the molecular weight is 78, and consequently the molecular formula C_6H_6. But when benzene is acted upon by chlorine the simplest derivative that can be obtained is C_6H_5Cl, and remembering that hydrogen and chlorine are of equal valency, it follows, from this absolutely different line of reasoning, that C_6H_6 again represents the molecular formula of this body. The determination of the atomic arrangement in this case is much more complex

than the one previously discussed, and here the theory of valency in the hands of Kekule gained one of its greatest victories. Without going into details, the proof that the hydrogen atoms are of equal value has been shown on the following general argument.

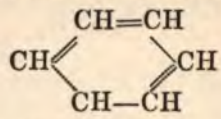
Representing the molecule as

$$C_6 \overset{1}{H}\ \overset{2}{H}\ \overset{3}{H}\ \overset{4}{H}\ \overset{5}{H}\ \overset{6}{H},$$

it has been proved that if one of the hydrogen atoms be replaced by the radical (OH), say No. 1, the resulting compound phenol

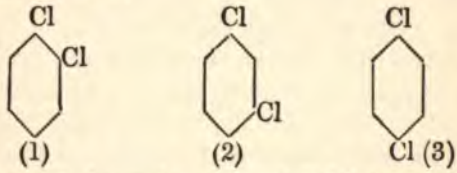
$$C_6 \overset{1}{(OH)}\ \overset{2}{H}\ \overset{3}{H}\ \overset{4}{H}\ \overset{5}{H}\ \overset{6}{H}$$

is identical with those obtained by replacing either 2, 3, or 4; it has been further proved that with respect to position numbered 1, those numbered 2 and 6 are identical, and also 3 and 5. Consequently, all the hydrogen atoms, and therefore the carbons to which they are joined, are symmetrically placed towards each other. Kekule aptly expressed this in the following constitutional formula:



Here, the latent valencies, as they have been previously termed, are represented by double bonds, a point which will be discussed in a later chapter, and may for the present be disregarded. This structural arrangement, whilst clearly showing the existence of but one mono-substitution product, gives further a complete explanation of the existence of three di-substitution derivatives, always provided, of course, that isomerism is not possible in the substituting group.

Dichlorbenzene, for instance, exists in three isomeric modifications, and representing the benzene nucleus as a hexagon, the structural formulae for these will be



The first is termed the ortho or 1 : 2-dichlorbenzene, the second

the meta or 1 : 3, and the fourth the para or 1 : 4, and since the most extended observations have shown that in such cases never more than three isomers are obtained, it follows that position 1 : 2 must be the same as 1 : 6, and 1 : 3 as 1 : 5. Ladenburg, however, subjected this to close investigation and conclusively proved that such was the case.

The characteristics of this closed-ring system are pronounced and very different from the open-chain hydrocarbons; the nucleus has been shown to be present in so many aromatic oils and resins that benzene and its derivatives are termed Aromatic, in distinction to the open-chain hydrocarbons which are called Aliphatic. Now, more perhaps for the sake of convenience than anything else, since the number of benzene derivatives is so enormous, these are usually studied separately from the aliphatic derivatives; but as the number of substances of both series described in this work is but a mere fraction of those discussed in any of the even moderately sized textbooks on Chemistry, the hydrocarbons and their derivatives, of both series, will be studied more or less together, when it is hoped that a better grasp of their similarities and many dissimilarities will be obtained.

Not only are such ring-shaped substances containing from three to seven carbon atoms known, but many containing carbon atoms replaced by other elements have been isolated, and some of these will be described in the following chapters.

B. GENERAL PHYSIOLOGICAL INTRODUCTION.

Practical therapeutics may be deductive or inductive; may, that is to say, be based on some general principles which in their turn depend on the conceptions held as to diseased processes and the pharmaco-dynamics of certain substances, or they may be merely the result of more or less discrete observations as to the curative value of such substances in certain diseased conditions. The former method is often spoken of as 'rational', and the latter as 'empiric'. In one of his lectures on Pharmacology the late Dr. Moxon, after pointing out this distinction, warned his hearers against 'reasonings in medical therapeutics'. 'Inductions' he continued, 'are commonly in harmony with the teachings of Physiology, but I advise you to hold them a good deal distinct from those teachings, and do not be too ready to allow them to rest, even in appearance, on those

teachings.' The lecture from which this passage is taken was delivered in 1874, six years after the publication of Crum Brown and Fraser's work on the curariform action of the ammonium bases, which appeared to be the beginning of a rational system of pharmacology. Physiological action determined on general principles by a study of chemical composition, an exact adaptation of means to ends, and the disappearance of empirical medication seemed not impossible achievements after a beginning had once been made by this important and far-reaching generalization. Moxon, however, was a determined empiric, not owing to any aversion to scientific method, but because he saw that our fundamental knowledge of facts was not sufficiently large to support any superstructure of a general or theoretical character. Although remarkable advances in Pharmacology have been made during the last half century, the practical position now is not greatly changed since Moxon's lecture. Schmiedeberg, writing in 1902, said: 'The relation of Therapeutics to Pharmacology is obvious, in so far as the former is based on a scientific foundation. This, however, is very far from being the case. Everywhere, pristine empiricism is master, entirely unconfined by any scientific barriers.' There are not wanting, however, signs that although empiricism must for many years longer dominate our treatment of diseased conditions, yet there is a growing interest in the subject of rational therapeutics, and a wider appreciation of the advantages which an extended knowledge of the matter would ensure. Not only has a vast amount of research been devoted to elucidating such relationships as may exist between the chemical structure of a drug and its physiological action, but, in addition, some space is devoted to these topics in textbooks and in the medical press; moreover, there is already a large industry established, though not indeed in this country, which has for its object the production of synthetic drugs, the action of which is more or less accurately predicted from their chemical constitution.

We may, therefore, allude to the obstacles which have prevented a still greater expansion of the domain of rationalism, and a more complete abandonment of the therapy of empiricism. The difficulties in correlating chemical and physiological properties fall into two main divisions, the first has reference to the drug itself, and the second to the organism on which it is intended to act.

Various physical characteristics, such as solubility and volatility, markedly influence and alter the action of a drug, and interfere

with the development of its action. Upon these depend, in part at least, speed of absorption and excretion; a decrease in the former or an increase in the latter will generally mean a decrease in physiological activity. The effect of solubility is seen in the hypnotics chloral hydrate and sulphonal. The former is soluble and rapidly absorbed, and consequently rapidly produces its physiological effect; the latter, owing to its slight solubility, is slowly absorbed and hence the physiological action is delayed, but also prolonged, and drowsiness may persist for many hours after the administration of that substance.

The physiological inactivity of the higher members of many homologous series, such as the alcohols or acids, is attributable to their insolubility, which renders them incapable of being absorbed.

The important question of solubility in fatty substances will be dealt with in the chapter on Narcotics.

The degree of dissociation which a substance undergoes on solution in water can play an important part in its action on the organism. But organic substances, with which alone this work deals, are, with the exception of certain groups such as the acids, generally undissociated on solution. The case of the mercury salts may, however, be given as an illustration of this phenomenon.

Paul and Krönig investigated the disinfectant power of mercuric chloride, $HgCl_2$, bromide, $HgBr_2$, and cyanide, $Hg(CN)_2$, using the spores of B. Anthracis, and found that in equimolecular solutions the chloride was the most powerful antiseptic, then the bromide, and that the cyanide had least action. This corresponds to the degree of dissociation which takes place in the three solutions. The character of the metallic ion is, of course, of primary importance, as salts of other bases which are still more dissociated in solution have not the same disinfectant action as those of mercury.

An instructive insight into the difficulties of the problem is further afforded by the researches of the same authors into the disinfectant powers of a solution of perchloride of mercury and common salt. Many years ago, Bacelli, when advising intravenous injections of mercurial salts in cases of syphilis, employed a solution of the perchloride mixed with sodium chloride in the proportion of one to three, which he stated was more effective in actual practice. Paul and Krönig have shown that the actual process is as follows:— A double salt (Na_2HgCl_4) is formed, which dissociates into positive sodium ions and negative complex ions of mercury and chlorine. The latter are inactive from an antiseptic point of view, but a cer-

tain amount of secondary dissociation of the complex negative ion occurs, resulting in the formation of the active mercury ions, though to a smaller extent than when an equimolecular solution of mercuric chloride alone is employed. The action is thus hindered, but in practice the increased solubility which is obtained by the addition of salt more than counterbalances the decreased ionic dissociation. On the other hand, salicylic acid, which is only very slightly dissociated on solution and consequently is a very weak acid, owes its bactericidal action to the entire molecule and not to the ions. Sodium salicylate, which is largely dissociated, when dissolved in water shows no antiseptic properties.

That the velocity of diffusion of a substance will play an important part in its physiological reactivity is clear, and to this factor may be ascribed, for instance, the differences observed in the group of digitalis glucosides. The most powerful member of this group is digitoxin, a very insoluble crystalline substance. Cloëtta has introduced an amorphous and soluble form of digitoxin which has been named *digalen*: following, in all probability, on increased solubility there is increased diffusibility, and to this is attributed the absence of digestive disturbances when it is administered by the mouth.

Two further points may be mentioned as of practical importance, which render the issues of pharmacological experiment difficult to determine. The first of these is the erroneous impression as to the main action of a drug which may be produced by certain bye effects. An extreme instance of this is alcohol, which is commonly known as a stimulant and is frequently taken to produce a feeling of warmth, whereas its chief physiological actions are those of a narcotic and antipyretic. The second is the effect of dosage. Many bodies produce varied effects according to the doses in which they are administered. This, of course, does not depend on any real alteration in the physiological character of the drug, but is merely a matter of distribution. A narcotic drug, for example, when given in doses large enough to produce sleep, may fail to exhibit certain secondary actions which are produced independently of the effect on the central nervous system. On the other hand, a substance with a specific action on particular organs, if given in toxic doses, may cause general symptoms which entirely mask the particular and characteristic effect.

Thus chloroform in narcotic doses causes a fall of temperature, which might be merely the result of muscular relaxation coupled with vasodilatation and increased heat loss. But it has been shown

that this fall of temperature is partly dependent on a direct action of the drug, which, apart from its narcotic powers, has an inhibiting effect on oxidation processes. In this it differs from ether, though there is also a fall in temperature during ether narcosis.

The main obstacle, however, to a rational appreciation of pharmaceutical actions lies in our ignorance of the chemistry and reactivity of the living cells. To attempt to calculate the result of a chemical interaction in which the constitution of only one of the bodies concerned is known, is obviously an undertaking destined to only a partial measure of success: but this is what is done when attempts are made to set forth the chemical basis of the action of drugs.

Complete explanations, in the proper sense of the word, are not at present possible, but starting from the better-known factor, that is, the drug, it is possible by introducing chemical variations of a definite character to modify the pharmacological results, and thus in some instances to gain an insight into the chemical influences which can be brought to bear on living cells.

We will now proceed to consider in detail the two variants in any pharmacological process, namely (A) the cell protoplasm, and (B) the drug.

(A) With respect to the protoplasm, the theory of Oscar Loew is of considerable interest. He divides the general poisons into 'oxidizing,' 'catalytic,' 'salt-forming,' and 'substituting.' These in sufficient concentration, act on all living protoplasm, and depend for their activity on the chemical character of the substances of which living cells are composed.

The special poisons, forming the second main group, comprise those which only act on certain classes of organisms. Under this head are included the toxins, the antitoxins, and similar bodies, the action of which is specific for certain kinds of protoplasm; the organic bases (including the alkaloids) which probably act by disturbing the structural character of certain cells; and the indirect poisons which make respiration impossible, &c.

Now as regards the general poisons, the first three classes are not important for our present purpose. The first includes bodies such as ozone, peroxide of hydrogen, chromic acid, permanganates, hypochlorites, phosphorus, &c. Among the catalytic, i. e. those which influence chemical action without undergoing any apparent change themselves, are the aliphatic narcotics, which will be dealt with later on in the present work. The third group owes its

existence to the amphoteric character of protein, and includes acids, the soluble bases such as alkalies and alkaline earths, and the salts of the heavy metals.

The fourth class includes a number of bodies which even in extreme dilutions can react with aldehydes and amines, forming substitution products—whence the name. The more readily this reaction takes place the more powerful will be the toxic effect. Examples may be found, firstly in hydrazine and phenylhydrazine, which most readily combine with aldehydes and are consequently powerful poisons; similarly, hydroxylamine, aniline and free ammonia. Secondly, the phenols and their derivatives, especially the amidophenols; and thirdly, prussic acid, sulphuretted hydrogen, and the acid sulphites—all substances capable of reacting with aldehyde groups.

As a general rule, primary amines (not of the aliphatic series) are more reactive than secondary, and these more so than tertiary. Pyridine, with a tertiary nitrogen atom, is much less toxic than piperidine, which contains an NH group. Xanthine, with three NH groups, is more toxic than theobromine with two such radicals. Methyl aniline has a different but weaker action than aniline.

The amido group is readily attacked by nitrous or nitric acids, by aldehydes, ketones, &c.

Loew gives many examples selected from among those bodies which are protoplasmic poisons, and shows generally that toxicity increases *pari passu* with reactivity.

Thus Loew explains the very various chemical structures of these general protoplasmic poisons, by showing that they will all react with one or two very labile groups which he believes are present in the living protoplasmic molecule, but undergo a chemical change and become stable when the protoplasm dies. Consequently, these general poisons have no action on dead protein, so differing from bodies like the mineral acids, which are equally destructive to living or dead tissues.

Though considerations of this sort may help towards elucidating certain general reactions, they completely fail to account for what is generally known as the selective action of drugs.[1] From our present point of view, it should perhaps be more correctly stated as

[1] Drugs having a selective action are classed by Loew under 'special poisons'. An important group among them, the Alkaloids, will be dealt with in detail in a subsequent chapter, and Loew's theory in general will be criticized in the chapter on organic dyes.

the selective action of cells. The most specialized poisons—such as cocaine or strychnine—are capable of reacting with a great number of different sorts of cells, but within the body certain cells appear more and others less susceptible, and hence the special train of symptoms, for example, which follows the introduction into the body of the various alkaloids.

That the structure of the cytoplasm varies is seen by reference to many histological observations. The well-known differences in staining-reaction of different kinds of cells and in different parts of the same cell are examples in point. Thus, methylene-blue stains axis cylinders, the spiral fibres in ganglion cells and the sensory nerve endings, whereas the straight processes of the cells are unstained, and, as a rule, the motor nerve endings. Neither fuchsin, methyl-violet, nor safranin stains the axis cylinders.

The toxic proteins or toxins very closely resemble the alkaloids in their manner of action on the body cells and it is therefore, perhaps, hardly remarkable that the well-known side-chain theory of Ehrlich should be applied to both these groups. Thus the anterior cornual cells in the cord may be supposed to possess certain side-chains which render them specially capable of uniting with strychnine, and those of the central cortex similar side-chains ready to unite with morphine.[1] Kobert's paradox, that the more powerful the drug and the more marked its effects, the less is any chemical change to be detected in its passage through the body, is probably more apparent than real. It is true that, whereas certain substances which are hardly toxic at all are completely decomposed, others, with minute lethal doses, can be recovered unchanged in the urine. There is not wanting, however, an increasing amount of evidence that in reality minute quantities of such bodies as the alkaloids are retained in the body, and probably take part in some chemical reaction which may or may not be of a catalytic nature. Thus atropine is said to be oxidized in the body to the extent of two-thirds of the dose given.

It is necessary, as Schmiedeberg points out, to extend to the word 'chemical' a very wide significance. It must, in fact, include all those changes which are commonly called physico-chemical; the cell itself, containing protein, lecithin, salts, water, &c., may be looked upon as a physico-chemical combination in a state of equilibrium, upon which depends its vital activity. The most characteristic properties of the cell are those which depend on

[1] See note at end of chapter.

the integrity of the protein portion, concerning which we can only say that it is too labile to admit of examination in a living condition.[1]

(B) When we turn to the second factor in pharmacological reactions, namely, the drugs, our survey of the subject may conveniently be divided into two parts. In the first place, we may notice certain generalities connected with physiological activity which have been arrived at by the experimental method, and then we may go on to consider the theoretical views which have been expressed as to the way in which drugs exhibit their particular actions in the animal body.

I. In correspondence with their comparatively slight chemical reactivity, the aliphatic series of bodies do not on the whole possess powerful pharmacological actions. Brunton and Cash state that the predominant feature of the lower members of the fatty series is their stimulant and anaesthetic action on the nerve centres (frogs). Schmiedeberg collects in a general class the narcotics of the aliphatic series as (1) the Alcohol and Chloroform group. This includes the gaseous and fluid hydrocarbons, the monatomic alcohols and their ethers, ketones, aldehydes, and their halogen derivatives. These are mainly characterized by their action on the cerebrum producing narcosis. They will be considered in detail in subsequent chapters. (2) The Ammonia derivatives, on the other hand, are characterized by a convulsant action on the cells of the spinal cord.

When the triad nitrogen, by the addition of another alkyl group is converted into pentad nitrogen, a remarkable change in the physiological action occurs, which was first pointed out by Crum Brown and Fraser in 1868, subsequently confirmed by Brunton and Cash, and very fully illustrated by many observers. All the quaternary ammonium bases have a curare-like action, paralysing the motor nerve endings. Numerous illustrations of this principle will be found in the course of the present work.

II. The aromatic bodies being chemically more reactive are physiologically more effective. Experiments with frogs showed that the members of the aromatic series, like the aliphatic, affect the nervous system, but they appear to affect motor centres more than sensory, so that instead of producing anaesthesia, like members of fatty series, they tend rather to give rise to tremor, convulsions, and paralysis (Brunton and Cash). The activity is, however, increased by the substitution of hydrogen. In this case, alterations

[1] *Pharmacologie*, 1902.

in physiological action may be produced not only by alterations in the molecule as a whole, but by variations in the group which substitutes hydrogen. Examples of this will be considered in the chapter on the Alkaloids, which are all heterocyclic bases with various side chains. Especially important in this connexion is the rule enunciated by Kendrick and Dewar, that the introduction of hydrogen into the cyclic bases in all cases increases their physiological action, and thus their toxicity.

In a general sense, also, Dujardin-Beaumetz and Bardel's conceptions of the influence of various side groups on the benzene compounds may be taken as accurate:—

(i) Those containing hydroxyl are antiseptic.

(ii) Those containing an amido group or an acid amide are hypnotic.

(iii) Those containing both an amine group and an alkyl group are analgesic.

These few general rules will be found subject to variation and exception, due to one or more of those disturbing factors which have already been noted; but they show by their very existence that within certain limits it is possible to modify the physiological action of a drug at will in a given direction. Other 'rules' of less general applicability will be noted under the various groups of compounds which will be discussed in subsequent chapters.

We have already dealt with the mechanism of interaction between the living cell and the drug from the point of view of the cell, as far as anything can be definitely stated about the matter; a little more may now be said regarding the drug.

The action of a drug appears to depend upon its possessing, firstly, some group of atoms capable of exerting a specific effect on the cell, and secondly, another group or side chain capable of entering into some kind of chemico-physical relationship with certain cells, whereby the first is enabled to produce its action. This second is commonly known as the anchoring group. The term 'chemico-physical' was used advisedly, as it cannot be said to be definitely settled whether a chemical reaction in the ordinary sense really takes place. P. Ehrlich has compared the reaction which is supposed to take place with those postulated by Witt for the organic dyes. The dyeing properties of a substance are dependent on the presence of certain atomic groupings which are termed colour groups or chromophores. The entrance of the chromophore group into a molecule results in a derivative more or less coloured,

but lacking the characteristics of a dye, and it is only when basic or hydroxyl radicals (auxochrome) are further introduced, that the dyes result. For example, in azo-benzene $C_6H_5 . N : N.C_6H_5$ the group N_2 is the chromophore. The substance which is coloured (red) Witt termed the chromogene; it is not a dye, but becomes one on the introduction of a basic group, e. g. $C_6H_5 . N : N.C_6H_4(NH_2)$.

Anthraquinone

$$C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle C_6H_4$$

is colourless (chromogene), but on the introduction of two hydroxyl groups, the dye alizarin results

$$C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle C_6H_2(OH)_2.$$

Two groups are consequently necessary to confer on a substance its dyeing properties; further, the colour itself is dependent on the number and nature of the—say—basic radicals; thus, amido-azo-benzene, $C_6H_5 . N : N.C_6H_4(NH_2)$, is yellow, the di-amido derivative is orange, the tri-amido brown.

Many drugs can be extracted unchanged from the tissues, and Ehrlich regards them as having been withdrawn from solution and existing there in a state of, possibly, solid solution—in a corresponding manner to a dye. A dye is also withdrawn from solution by a cellular material, and Witt regards it as forming a solid solution from which it may be again withdrawn by the use of a more powerful solvent. But it is much more probable, as Freudlich and Losev have shown, that since Henry's law does not hold for dyestuffs, the phenomenon of dyeing is one of adsorption, and with this may be compared the views expressed in the chapter on Narcotics as to the manner in which the drug enters the cell.

The non-toxicity of acidic substances is traced to the fact that they are no longer capable of being absorbed by the tissues. Ehrlich has shown that those dyes which stain the brain tissue cease to do so on conversion into sulphonic acids, as neurotropic substances lose their characteristics on the entrance of such groups.

He also suggests that the analogy between the physiological action of substances and the theory that has been sketched of the dyes, may be of value in the synthetic production of drugs. Substances with the power of acting on definite cells may be found (myotropic, neurotropic, &c.), and the character of their action controlled by the introduction of groups (chromophore) of varied pharmaco-dynamic effect.

The selective action of a drug, which has already been referred to from the opposite point of view, may in some instances be explained by its solubility in lipoid substances. This question will be discussed in full in a later chapter (see p. 83).

This outline of the present position of the question as to the relationships between chemistry and pharmaco-dynamics, will at least show that, whereas in many instances and by many various ways a close relationship may be shown to exist, there is as yet no possibility of the abandonment of empiricism in practical medicine. Though much has been done much more remains, and though the principle has been demonstrated its limits are yet to be defined and the details of its action delineated. Whether these details will be rather of a chemical or physical character cannot at present be stated. The various sciences are, after all, only aggregates of convenience, and the boundaries which divide their territories become less and less distinct the nearer we get to the actual nature of things. The pharmacologist is merely concerned with the correlation of the phenomena of physiology with those of the intimate constitution of matter, whether that constitution be determinable by physics or chemistry, or an indistinguishable combination of both.

NOTE.—Ehrlich has always insisted on the differences which exist between the action of a toxin and that of a drug the chemical formula of which is known, and for some time was inclined to deny that it was possible to suppose any similarity in the mechanism by which the toxin and the drug are anchored to the cell.

Recently, however, he has somewhat modified his views in the matter and now postulates groups or side-chains called *chemio-receptors* by which the corresponding haptophoric groups of the drug are united to the cell body.

These chemio-receptors are supposed to differ from ordinary receptors in being less intimately analogous to the nutritive apparatus of the cell, and in being less capable of an independent existence; hence they cannot be thrown off as anti-bodies, nor are they increased in number when small doses of a drug are administered over a long period of time.

CHAPTER II

A. The Aliphatic and Aromatic Hydrocarbons. Their methods of preparation and properties. Methods used in the synthesis of their derivatives. B. Physiological Characteristics of the Hydrocarbons. Effect on Physiological reactivity of the introduction of Methyl and Ethyl groups, of unsaturated condition of the molecule, and of Isomeric and Stereo-isomeric relationships.

A. ALIPHATIC AND AROMATIC HYDROCARBONS.

The hydrocarbons are a number of compounds of carbon and hydrogen which have been classified into various groups owing to the striking differences that have been found to exist between them.

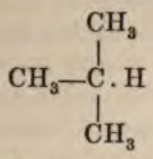
Paraffin Hydrocarbons.

The simplest series commences with methane, CH_4, and related to this, and possessing its general characteristics, are a large number of what have been termed the methane or limit hydrocarbons, or, owing to their great stability, the paraffins. They form what is termed an homologous series—one in which each member differs from the next by a constant quantity, viz. CH_2.

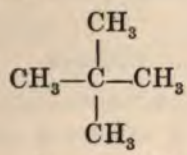
Methane	CH_4	} gases.
Ethane	C_2H_6	
Propane	C_3H_8	
Butane	C_4H_{10}	B. P. 1°
⋮		
n. Hexane	C_6H_{14}	B. P. 71°
⋮		
Tetradecane	$C_{14}H_{13}$	M. P. 5·5°
⋮		
Di-myricyl	$C_{60}H_{122}$	M. P. 102°

One general physical property of such a group is that as the molecular magnitude increases the members of it pass from the gaseous to the liquid phase, from liquids of low boiling-point to those of high, or from liquids of high boiling-point to solids of low melting-point as the case may be. This series only contains singly linked carbon atoms, and since the limit of saturation by

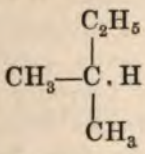
hydrogen has been reached, they are frequently called the limit hydrocarbons. Isomerism first appears in butane, C_4H_{10}, and the theory of valency satisfactorily accounts for the existence of two substances of that formula, having the same vapour density and molecular weight, but differing physical and chemical properties, viz., *n*-butane, $CH_3.CH_2.CH_2.CH_3$, and *iso*-butane,



The *n*- or normal derivations are those consisting of a chain of carbon atoms, whilst the *iso*- have a branched structure. But since this latter nomenclature may not be sufficiently precise, such hydrocarbons may be regarded as derivatives of methane; thus, *iso*-butane may be termed tri-methyl-methane. This is, perhaps, clearer in the case of pentane. *n*-Pentane is $CH_3.CH_2.CH_2.CH_2.CH_3$, two *iso*-pentanes exist; if the first



is termed tetra-methyl-methane, and the second ethyl-di-methyl-



methane, their respective structures are at once evident.

Occurrence in Nature. Many of these hydrocarbons occur in nature. Methane, or marsh gas, formed by the decay of organic substances, is found in the coal measures, and in regions like Baku in the Caucasus, and in the petroleum districts of America. Large deposits of petroleum, consisting of mixtures of members of this series, are found in America, Russia, Alsace and Hanover. That from America consists almost exclusively of normal paraffins. The fractions boiling between 50°–60° consist chiefly of pentane and hexane, between 70°–80° hexane and heptane, between 90°–120° heptane and octane. Refined petroleum or kerosene boils

at 150°–300°. The solid high-boiling paraffins are more abundant in the petroleum from Baku than in that from America, and are also obtained by the distillation of the tar from turf, lignite, and bituminous shales.

Paraffins that liquefy readily and fuse between 30° and 40°, are known as vaselines and employed as salves.

Properties. All the members of this group are insoluble in water; the lower are soluble in alcohol and ether, but the solubility diminishes as the molecular weight increases. They are characterized by their great stability and consequent slight reactivity. Fuming nitric or even chromic acid does not affect them in the cold, and on heating the action is but slow. Chlorine and bromine give rise to substitution products, a characteristic property of the saturated hydrocarbons. Methane, for instance, gives firstly methyl chloride, CH_3Cl, then CH_2Cl_2, $CHCl_3$, and finally CCl_4, in which all the hydrogen atoms have been replaced by chlorine; in such reactions, for every atom of chlorine that enters the molecule an atom of hydrogen is removed in the form of hydrochloric acid, e.g. $CH_4 + Cl_2 = HCl + CH_3Cl$, and so on.

Olefines.

The next group of hydrocarbons contains two hydrogen atoms less than those just considered, and forms an homologous series, with physical properties similar to the paraffins. When the structure of, say, the simplest member, ethylene, is considered, it is seen that apparently carbon is acting as a trivalent element, thus $CH_2 . CH_2$. But all the members of this series, quite unlike the paraffins, are very reactive and possess the following properties: They absorb a molecule of chlorine, bromine, and iodine, without the formation of the corresponding halogen hydride. In a similar manner, molecules of hydrogen or the haloid acids are readily added, and these reactions usually take place with considerable ease. The explanation that is offered of these phenomena is the assumption that the fourth valencies of each carbon atom mutually saturate each other, graphically described by a double bond, e.g. $H_2C = CH_2$, or $CH_2 : CH_2$ and the substance is said to be *unsaturated*. The reactions alluded to being expressed by the following equations:—

$$CH_2 : CH_2 + Cl_2 = CH_2Cl . CH_2Cl.$$
$$CH_2 : CH_2 + H_2 = CH_3 . CH_3.$$
$$CH_2 : CH_2 + HI = CH_3 . CH_2I.$$

The chief characteristic, then, of the olefine hydrocarbons is the ease with which they become saturated, i. e. pass back into the limit hydrocarbons or their derivatives. The graphic mode of representation must not be understood to mean a more stable state of union of the two halves of the molecule; it is rather the contrary, such a state of combination generally indicating less stability, since it is at that point that the molecule is first attacked by reagents. It will further be noticed, in the following chapters, that this state of combination usually confers a rise in toxicity, above that of the corresponding saturated substance; this certainly depends on the much greater chemical reactivity of such groupings.

The members of this series are absorbed by sulphuric acid, ethylene giving ethylsulphuric acid,

$$\begin{matrix} CH_2 \\ \| \\ CH_2 \end{matrix} + SO_2\begin{matrix} OH \\ OH \end{matrix} = SO_2\begin{matrix} O.C_2H_5 \\ OH \end{matrix}$$

and through the agency of this substance alcohol and ethers may be obtained by the action of water or alcohol, e. g.

$$SO_2\begin{matrix} O:C_2H_5 \\ OH \end{matrix} \quad \begin{matrix} OH:H \\ + \end{matrix} \quad = \quad SO_2\begin{matrix} OH \\ OH \end{matrix} + C_2H_5OH$$

Ethyl alcohol.

and

$$SO_2\begin{matrix} O:C_2H_5 \\ OH \end{matrix} \quad \begin{matrix} C_2H_5O:H \\ + \end{matrix} \quad = \quad SO_2\begin{matrix} OH \\ OH \end{matrix} + C_2H_5.O.C_2H_5$$

Ethyl ether.

Acetylenes.

In this homologous series, the first member, acetylene, is the most important; it contains two hydrogen atoms less than ethylene, and for reasons similar to those previously mentioned the existence of three double bonds is postulated, and the substance said to be doubly unsaturated, e. g. HC:CH. The reactivity of members of this group is quite similar to that of the previous. They absorb one molecule of hydrogen, giving ethylenes, e. g.—

$$CH:CH + H_2 = CH_2:CH_2$$

which then absorb a second, passing over to paraffins, e. g.

$$CH_2:CH_2 + H_2 = CH_3.CH_3.$$

The reaction with the halogens is similar, chlorine for instance gives dichlorethylene and then tetrachlorethane,

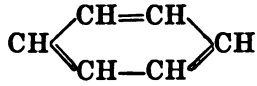
$$\begin{matrix} CH \\ \| \\ CH \end{matrix} + Cl_2 = \begin{matrix} CHCl \\ \| \\ CHCl \end{matrix} + Cl_2 \rightarrow \begin{matrix} CHCl_2 \\ | \\ CHCl_2 \end{matrix}$$

Tetrachlorethane.

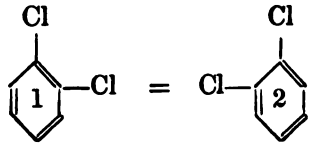
Acetylene and many of its derivatives are characterized by the formation of solid silver and copper compounds, which when dry are extremely explosive. These may be employed for the detection and isolation of the acetylenes, since on treatment with hydrochloric acid the pure hydrocarbon is liberated. Acetylene itself is at present prepared in large quantity by the action of water on calcium carbide and is used for illuminating purposes.

Benzene hydrocarbons.

The last series of hydrocarbons may be regarded as derived from the simplest member, benzene, by means of the replacement of one or more of the hydrogen atoms by the residues of the aliphatic series. The constitutional formula assigned to the parent hydrocarbon by Kekule, viz.



is in agreement with most of its properties and those of its derivatives, as previously indicated. But when the nature of the alternate double and single bonds is investigated it becomes at once apparent that phenomena of a different order appear with the formation of this closed-ring system. In this case, the double bond bears no similarity to that previously discussed. For instance, the action of chlorine on benzene gives rise to substitution products such as C_6H_5Cl or $C_6H_4Cl_2$, and not to addition derivatives, as might have been expected had the unsaturated nature of the molecule been akin to that of ethylene. Moreover, had this double union been analogous to that previously discussed, the compounds 1 : 2 and 1 : 6 should be different, whereas they are identical, e. g.

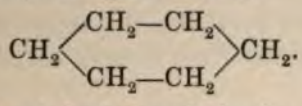


for, in the first case, between the two carbon atoms carrying the chlorine atoms there exists one of these double bonds, which is absent in the second. In a corresponding case in the open-chain ethylene derivatives, these two chlorine substitution products would have been different, i. e. isomeric.

It may be put in a different way as follows: There is but little difference between the two hydrocarbons *n*-hexane,

$$CH_3 . CH_2 . CH_2 . CH_2 . CH_2 . CH_3 ,$$

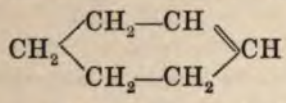
and hexamethylene, or, hexahydrobenzene,



Further, the unsaturated ethylene derivative

$$CH_3 . CH_2 . CH_2 . CH : CH . CH_3$$

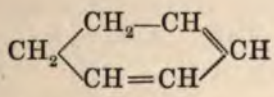
has the same general characteristics as tetrahydrobenzene,



that is, the behaviour of the two towards the halogens, halogen hydrides, &c., is similar to that previously described. Then with the di-ethylene,

$$CH_3 . CH : CH . CH : CH . CH_3 ,$$

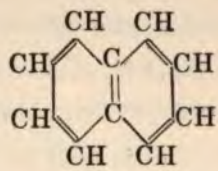
and dihydrobenzene,



much about the same relationship holds true, both have the general properties of di-ethylene derivatives. But when the third double linkage is introduced and dihydrobenzene becomes benzene, these general properties disappear and are replaced by entirely different characteristics. The entrance of the radical of this hydrocarbon, termed phenyl, into various molecules, results in changes in the physical, chemical and physiological properties of quite a different order from those produced by the corresponding entrance of aliphatic radicals: as a result appear what are termed the *negative characteristics* of the benzene nucleus, phenomena which will be studied in detail, in relation to physiologically active substances, in the following chapter.

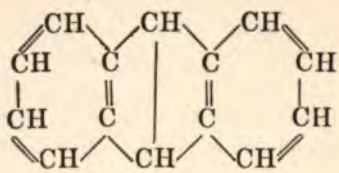
Sources. Not only benzene but numerous other derivatives are obtained by the dry distillation of coal. They are present in coal tar, which is produced in enormous quantities in the manufacture of coal gas. Among the homologues found are toluene or methyl benzene, $C_6H_5.CH_3$, the three dimethyl benzenes or xylenes, $C_6H_4(CH_3)_2$ and the three trimethyl benzenes, $C_6H_3(CH_3)_3$.

Among the higher boiling fractions of coal tar, many more highly condensed aromatic hydrocarbons are found; of these, naphthalene, $C_{10}H_8$, and anthracene, $C_{14}H_{10}$, are the only two that will be discussed. The former shows great similarity to benzene, from which it differs by C_4H_2. Its deportment is satisfactorily explained by the constitutional formula suggested by Erlenmeyer,



It consists of two benzene nuclei, having in common two carbon atoms occupying the ortho position.

Anthracene is the parent hydrocarbon of a series of vegetable compounds of which the most important is the dye alizarine. The following formula expresses its relationship to benzene and its various syntheses,



Oxidation and Reduction. The chief characteristic of the benzene hydrocarbons is the great stability of the ring complex; in the vast majority of reactions undergone by its derivatives the nucleus itself is not destroyed. This feature distinguishes the aromatic substances from the derivatives of the methane and other open-chain series. As a very general rule, oxidation or reduction can be carried on without tearing this ring asunder. In the former process the benzene homologues have their side chains oxidized to (COOH) which occupies the position of the substituting group. This con-

sequently affords a method of distinguishing between isomeric derivatives. Thus the three xylenes,

$$C_6H_4\begin{matrix}CH_3\\CH_3\end{matrix}\ 1:2,\ 1:3 \text{ and } 1:4,$$

are isomeric with ethyl benzene, $C_6H_5 . C_2H_5$; on oxidation, 1 : 2-xylene gives phthalic acid,

$$C_6H_4\begin{matrix}COOH\\COOH\end{matrix}\ 1:2,$$

the meta isomer gives the corresponding 1 : 3 di-carboxylic acid, and the para, 1 : 4 di-carboxylic or terephthalic acid ; on the other hand, ethyl benzene gives benzoic acid $C_6H_5 . COOH$. Of the three di-carboxylic acids mentioned above, only the ortho gives an anhydride,

$$C_6H_4\begin{matrix}CO\\CO\end{matrix}O$$

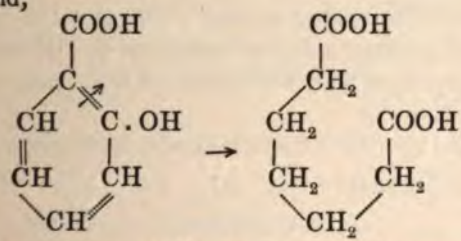
this being due to the proximity of the two reacting groups.

Similar peculiarities to this will be noticed among a large number of ortho substituted benzene derivatives, so much so that the interaction of two such groups with each other, or with another substance to form a closed chain, can be generally taken as a proof that they occupy adjacent positions (i. e. ortho) in the nucleus.

The reduction of benzene is much more difficult than that of the unsaturated open-chain hydrocarbons. Benzene itself, heated to a high temperature with hydriodic acid, gives hexamethylene,

$$CH_2\begin{matrix}CH_2—CH_2\\CH_2—CH_2\end{matrix}CH_2.$$

Salicylic acid reduced by sodium in amyl alcohol solution gives *n*-pimelic acid,



Such a breakdown of the benzene nucleus, as in this latter case, resulting in the final substance possessing the same carbon

content as the original, is, relatively speaking, extremely rare. Powerful oxidizing agents, of course, effect complete decomposition, the invariable rule in carbonaceous compounds; but in those cases where the nucleus itself is attacked, the resulting derivative has generally a less carbon content than that of the benzene derivative experimented upon.

General Methods used in the Preparation of the Hydrocarbons.

Since the hydrocarbons are the parent substances of all other organic bodies, their syntheses are of especial interest, and although the methods that may be used for their preparation are many, the following are the more important. A few, such as acetylene, can be obtained by the direct union of their elements, but the majority are formed by the union of simpler hydrocarbon nuclei.

1. **Hydrocarbons of the Paraffin and Benzene** series can be obtained by heating a mixture of the sodium salt of the acid with caustic soda.

$$\underset{\text{Sodic acetate.}}{CH_3.COONa} + NaOH = Na_2CO_3 + \underset{\text{Methane.}}{CH_4}$$

$$\underset{\text{Sodium benzoate.}}{C_6H_5.COONa} + NaOH = Na_2CO_3 + \underset{\text{Benzene.}}{C_6H_6}$$

2. The Würtz synthesis consists in acting upon the iodo or bromo derivatives of the hydrocarbons, in etherial solution, with metallic sodium

$$\underset{\text{Ethyl iodide.}}{C_2H_5.I} + Na_2 + I.C_2H_5 = 2NaI + \underset{n\text{-Butane.}}{C_2H_5.C_2H_5}$$

As a rule, the iodine derivatives react best, and the reaction proceeds better with primary halogen derivatives (i. e. those containing the . CH_2X group) than with secondary (: CHX), and seldom with tertiary (: C—X).

Mixtures of halogen derivatives may also be employed, i. e.

$$\underset{n\text{-Iodo-butane.}}{CH_3.CH_2.I} + Na_2 + I.CH_2.CH_2.CH_2.CH_3 =$$

$$2NaI + \underset{n\text{-Hexane.}}{CH_3.CH_2.CH_2.CH_2.CH_2.CH_3}$$

Fittig further showed that a similar reaction could be employed for the preparation of **Benzene homologues.**

$$C_6H_5Br + Na_2 + IC_2H_5 = NaBr + NaI + C_6H_5 . C_2H_5$$

Brom-benzene. Ethyl-benzene.

$$C_6H_5Br + Na_2 + BrC_6H_5 = 2NaBr + C_6H_5 . C_6H_5$$

Diphenyl.

It may also be employed for the preparation of **Ethylene derivatives,**

$$CH_2 : CH . CH_2I + Na + ICH_3 = CH_2 : CH . CH_2 . CH_3 + 2NaI$$

Allyl iodide. *a*-Butylene.

$$CH_2 : CH . CH_2I + Na + ICH_2 . CH : CH_2 = 2NaI + CH_2 : CH.CH_2 . CH_2 . CH : CH_2$$

Diallyl.

Acetylene can also be obtained by acting on chloroform with sodium, or more conveniently on bromoform with finely divided silver.

$$CHCl_3 + 6Na + Cl_3CH = 6NaCl + \begin{matrix} CH \\ \| \\ CH \end{matrix}$$

The reaction has been further extended to the preparation of closed-ring hydrocarbons, termed the **Cyclo-paraffins,** which will not be further described, owing to the fact that they are of relatively slight importance as regards the questions to be discussed in this work. Two examples may be given.

$$CH_2\begin{matrix} CH_2Br \\ CH_2Br \end{matrix} + Na_2 = 2NaBr + CH_2\begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix}$$

Trimethylene or Cyclo-propane.

$$\begin{matrix} CH_2 . CH_2 . CH_2Br \\ | \\ CH_2 . CH_2 . CH_2Br \end{matrix} + Na_2 = 2NaBr + \begin{matrix} CH_2 . CH_2 . CH_2 \\ | \quad\quad\quad | \\ CH_2 . CH_2 . CH_2 \end{matrix}$$

Hexamethylene or Cyclo-hexane or Hexahydro-benzene.

The Würtz synthesis is consequently of very wide applicability, but is of the greatest importance in the preparation of the higher members of the saturated hydrocarbons. As regards the formation of benzene homologues, it has been largely replaced by the Friedel

and Crafts' method, which will be described later. Further, it will be seen that this synthetic process constitutes an excellent means of determining the constitution of the hydrocarbons.

3. Unsaturated hydrocarbons of the ethylene and acetylene series, as well as benzene homologues containing unsaturated carbon systems substituted in the nucleus, can readily be obtained by the action of an alcoholic solution of potash on the corresponding brom-derivative.

Ethylene.

$$\begin{matrix} CH_2H \\ | \\ CH_2Br \end{matrix} + K\,OH = KBr + H_2O + \begin{matrix} CH_2 \\ \| \\ CH_2 \end{matrix}$$

Ethylbromide.

Phenyl-ethylene.

$$C_6H_5CHBr.CH_3 + KOH = C_6H_5CH:CH_2 + KBr + H_2O$$

Brom-ethylbenzene. Styrol.

or for acetylene and its derivatives:

Acetylene.

$$\begin{matrix} CH_2Br \\ | \\ CH_2Br \end{matrix} + 2KOH = 2KBr + 2H_2O + \begin{matrix} CH \\ \| \\ CH \end{matrix}$$

Ethylene dibromide.

Di-phenyl-acetylene.

$$C_6H_5CHBr.CHBrC_6H_5 + 2KOH = 2KBr + 2H_2O + C_6H_5C:C.C_6H_5$$

Stilbene bromide. Tolan.

The reaction with alcoholic potash is of great value for the preparation, not only of such types of hydrocarbons as those mentioned, but also for unsaturated derivatives of the most varied nature.

As regards the preparation of **ethylene**, the removal of the elements of hydrobromic acid, or generally of the halogen hydrides, is often very similar to that of the elements of water. This hydrocarbon can be easily obtained by the dehydration of ethyl alcohol by means of sulphuric acid.

$$\begin{matrix} CH_2H \\ | \\ CH_2OH \end{matrix} \rightarrow \begin{matrix} CH_2 \\ \| \\ CH_2 \end{matrix} + H_2O$$

This method is usually adopted for its preparation, and, generally speaking, is the most convenient for the formation of all hydrocarbons of this series.

Outline of the Methods employed in the Synthesis of Derivatives of the Aliphatic Hydrocarbons.

Theoretically the hydrocarbons may be looked upon as the starting-point for the preparation of organic substances. Practically, however, this only applies to the aromatic series and not to the aliphatic. In this latter, the hydrocarbons themselves are, from a synthetic point of view, of little or no value. The great stability of the paraffins, or, in other words, their slight reactivity, has already been alluded to; they are attacked by the halogens with the formation of the corresponding halogen derivatives, and these are very reactive and of the greatest value in synthetic work. But the difficulty of limiting such a reaction, that is, of converting say methane, CH_4, into monochlor methane, CH_3Cl, and not at the same time into CH_2Cl_2 or $CHCl_3$ or CCl_4, together with certain practical objections, renders this operation by no means an easy one to carry out. The halogen derivatives are much more readily obtained from the alcohols, and consequently it is this class of aliphatic substances which is of importance in synthetic work. Methyl and ethyl alcohols are readily obtained in quantity, the former by the dry distillation of wood, and the latter by the fermentation of sugar. Among the products of the first process is acetic acid, which may further be prepared by the oxidation of ethyl alcohol, and from this oxidation product of the hydrocarbons another large and important series of derivatives can be obtained.

When the alcohols are acted upon by the halogen acids, they easily give their corresponding halogen derivatives, thus ethyl alcohol gives either ethyl chloride, bromide, or iodide, and of these three the first is the most and the last the least stable, or in other words, ethyl iodide is more reactive than the bromide, and the bromide more reactive than the chloride. This variation in stability is exactly what might have been expected, since hydrochloric acid, HCl, is more stable than hydrobromic, HBr, and this more so than hydriodic acid, and the organic derivatives mentioned may be looked upon as the organic salts of these acids.

In the following examples ethyl alcohol or ethyl iodide or bromide

will be taken as illustrations of the value of such derivatives in synthetic aliphatic chemistry.

A. Syntheses of Aliphatic Derivatives from the Alcohols or Acetic Acid.

i. On oxidation alcohols containing a primary group, i. e. $-CH_2.OH$ pass to aldehydes and then acids.

$$CH_3OH \rightarrow \underset{\text{Formaldehyde.}}{H.COH} \rightarrow \underset{\text{Formic acid.}}{H.COOH}$$

$$CH_3.CH_2OH \rightarrow \underset{\text{Acetaldehyde.}}{CH_3.COH} \rightarrow \underset{\text{Acetic acid.}}{CH_3.COOH}$$

ii. Acetic acid acted upon by phosphorus tri- or penta-chloride gives acetyl chloride.

$$CH_3.COOH + PCl_5 = HCl + POCl_3 + CH_3CO.Cl.$$

The resulting substance is extremely reactive, and is used for the purpose of introducing the acetyl group $(CH_3CO)'$ into a large number of bodies, e. g.

$$CH_3CO\dddot{C}l + C_2H_5O\dddot{H} = HCl + \underset{\text{Ethylacetate.}}{CH_3CO.OC_2H_5}$$

$$CH_3CO\dddot{C}l + \underset{\text{Ethylamine.}}{C_2H_5NH\dddot{H}} = HCl + \underset{\text{Ethylacetamide.}}{CH_3CO.NHC_2H_5}$$

$$CH_3CO\dddot{C}l + \underset{\text{Aniline.}}{C_6H_5NH\dddot{H}} = HCl + \underset{\text{Acetanilide or } \textit{Antifebrin}.}{C_6H_5NH.COCH_3}$$

iii. Calcium acetate distilled with calcium formate gives acetaldehyde.

$$(CH_3COO)_2Ca + (H.COO)_2Ca = 2CH_3.CHO + 2CaCO_3$$

iv. Calcium acetate distilled alone, or with the calcium salts of other organic acids except formic, gives rise to the group of bodies called ketones, substances used in the preparation of the sulphonals.

$$(CH_3COO)_2Ca = CaCO_3 + \underset{\text{Dimethyl ketone or acetone.}}{\begin{matrix} CH_3 \\ | \\ CO \\ | \\ CH_3 \end{matrix}}$$

or $(CH_3COO)_2Ca + (C_2H_5.COO)_2Ca = 2CaCO_3 + \begin{matrix} CH_3 \\ | \\ CO \\ | \\ C_2H_5 \end{matrix}$

Calcium propionate. Methyl-ethyl ketone.

v. Chloral and chloroform are both obtained from ethyl alcohol, although the latter may also be formed from acetone, a substance obtained in considerable quantity in the destructive distillation of wood.

B. Syntheses from the Halogen derivatives of the Hydrocarbons.

i. Ethyl iodide treated with silver hydrate or dilute aqueous potash passes over to ethyl alcohol.

$$C_2H_5I + AgOH = C_2H_5OH + AgI$$

ii. Acted upon by potassium cyanide, ethyl nitrile results.

$$C_2H_5I + KCN = C_2H_5CN + KI$$

This reaction is of considerable importance, since by means of it the length of the carbon chain can be increased, moreover the resulting substance is capable of undergoing several important changes. On saponification, i. e. treatment with dilute potash or acids, the nitriles absorb water and become acids.

$$C_2H_5CN + 2H_2O = C_2H_5COOH + NH_3$$

Propionic acid.

That is, starting with ethyl iodide, C_2H_5I, a substance containing two carbon atoms, propionic acid, containing three, is obtained.

On reduction, the nitriles become amines, thus

$$C_2H_5CN + 2H_2 = C_2H_5CH_2NH_2.$$

Now one of the general properties of primary amines, or those containing the $-CH_2NH_2$ group, is their decomposition by nitrous acid with the formation of alcohols, e. g.

$$C_2H_5.CH_2.NH_2 + HNO_2 = C_2H_5.CH_2OH + H_2O + N_2.$$

Consequently, starting with ethyl alcohol, the next higher member of the series, propylic alcohol, and so on, may be synthesized by such reactions.

iii. Acted upon by ammonia in alcoholic solution, ethyl iodide gives rise to a mixture of the substituted ammonias.

$$C_2H_5I + HNH_2 = HI + C_2H_5NH_2$$
Ethylamine.

$$C_2H_5I + HNHC_2H_5 = HI + (C_2H_5)_2NH$$
Diethylamine.

$$C_2H_5I + HN(C_2H_5)_2 = HI + (C_2H_5)_3N$$
Triethylamine.

and
$$(C_2H_5)_3N + C_2H_5I = (C_2H_5)_4N.I$$
Tetraethyl-ammonium-iodide.

iv. Ethyl iodide readily acts on finely divided zinc or magnesium, forming the metallo-organic derivatives. These are a particularly reactive group of substances, and may be employed in a variety of syntheses. The magnesium derivatives have, for the last six years, replaced the spontaneously inflammable zinc compounds.

With ethyl iodide the following reaction takes place in etherial solution:—

$$C_2H_5I + Mg = Mg\begin{matrix}I\\C_2H_5\end{matrix}$$

and the resulting compound may be employed for many syntheses, for example, for those of the secondary and tertiary alcohols.

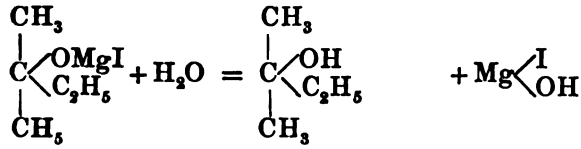
Magnesium ethyl iodide reacts with aldehydes such as acetaldehyde, CH_3CHO, and ketones, such as acetone, $CH_3.CO.CH_3$, according to the following reaction:—

$$CH_3.COH + Mg\begin{matrix}I\\C_2H_5\end{matrix} = CH_3.CH\begin{matrix}OMgI\\C_2H_5\end{matrix}$$

and
$$CH_3.CO.CH_3 + MgI.C_2H_5 = C\begin{matrix}CH_3\\OMgI\\C_2H_5\\CH_3\end{matrix}$$

and the resulting compounds are decomposed by water and dilute acids yielding secondary alcohols from the aldehyde, and tertiary from the ketones.

1. $$CH_3CH\begin{matrix}OMgI\\C_2H_5\end{matrix} + H_2O = CH_3.CH\begin{matrix}OH\\C_2H_5\end{matrix} + Mg\begin{matrix}I\\OH\end{matrix}$$
Methyl-ethyl-carbinol.

2. 

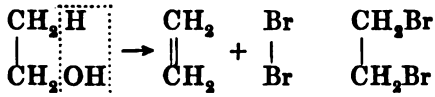
Dimethyl-ethyl-carbinol.

They can also be employed for the synthesis of saturated and unsaturated hydrocarbons, ethers, ketones, aldehydes, carboxylic acids, phenols, thiophenols, &c.

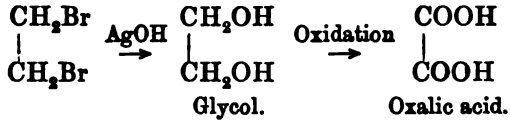
v. Symmetrical derivatives of ethane are usually prepared from ethylene dibromide

a substance which can be easily obtained by passing ethylene

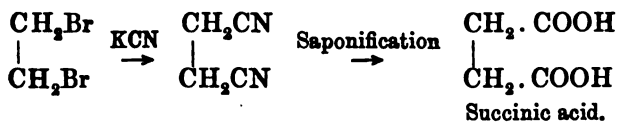
into bromine. This unsaturated hydrocarbon results from the dehydration of ethyl alcohol by means of sulphuric acid.



The bromide obtained by this reaction undergoes the same general reactions as those previously described, e. g.



Glycol. Oxalic acid.



Succinic acid.

The various synthetic reactions which can be carried out by means of acetoacetic ester or malonic ester will be found described in any textbook, but sufficient examples have been given to show clearly that it is not the paraffins themselves but their more reactive oxidation products or halogen derivatives which are employed in the preparation of members of the aliphatic series.

Outline of Methods employed in the Syntheses of derivatives of Aromatic Hydrocarbons.

The readiness with which the aromatic hydrocarbons take part in the most varied reactions sharply distinguishes them from the other group, and their reactivity is such that they constitute the practical foundation for the syntheses of the aromatic derivatives. The rapid and brilliant development of the chemistry of this group is largely due to the fact that the parent hydrocarbons are easily accessible in large amounts. They are present in coal-tar, in the tar from peat, and in smaller quantities in that from wood and bitumenous shales, and also in some varieties of petroleum.

Acted upon by nitric or sulphuric acids, the hydrocarbons of this series readily pass into nitro or sulphonic acid derivatives, and from these, but more especially the first, a large series of substances can be formed.

A. Nitrobenzene, $C_6H_5NO_2$, an example of the class of nitro derivatives, is formed quantitatively by acting on benzene with a mixture of nitric and sulphuric acid.

$$C_6H_5{:}H + OH{:}NO_2 = C_6H_5NO_2 + H_2O$$

By this means one group is very readily introduced into the nucleus, a second with more difficulty, and up to the present it has not been found possible to introduce more than three. Now nitrobenzene can be easily reduced to aniline, $C_6H_5NH_2$, by means of tin and hydrochloric acid or other similar reducing agents. This substance, which is the phenyl derivative of ammonia, lends itself particularly readily to a most varied series of synthesis. On solution in acids and treatment with nitrous acid at a low temperature the diazo substances are formed, e. g.

$$C_6H_5NH_2 . HCl + HNO_2 = C_6H_5-N\overset{N}{\underset{Cl}{\diagdown\!\!\!\!\diagup}} + 2H_2O$$

Diazobenzene chloride, produced in this reaction, is an explosive body, but its isolation is unnecessary since the following reactions are all carried out in solution.

i. On boiling with strong alcohol the hydrocarbons result.

$$C_6H_5 . N_2 . Cl + C_2H_5OH = C_6H_6 + N_2 + HCl + CH_3CHO$$

ii. Acted upon by cuprous bromide, chloride, or iodide, the corresponding halogen derivatives are formed.

$$C_6H_5 . N_2 . Cl \longrightarrow C_6H_5Cl + N_2$$

iii. On boiling with water the diazo group is replaced by hydroxyl.

$$C_6H_5.N_2.Cl + H_2O = C_6H_5OH + HCl + N_2$$

Phenol.

iv. If the diazo salt is acted upon by a solution of copper sulphate mixed with potassium cyanide, the nitriles are formed.

$$C_6H_5.N_2.CN \rightarrow C_6H_5CN + N_2$$

Benzonitrile.

v. On reduction phenyl hydrazine is formed. This substance is one of the most reactive among the aromatic derivatives, and will be described later.

$$C_6H_5.N_2.Cl + 4H = C_6H_5NH-NH_2.HCl$$

Phenylhydrazine hydrochloride.

vi. Acted upon by aniline, the diazoamido derivatives result.

$$C_6H_5.N:N.Cl + H.NHC_6H_5 = C_6H_5.N:N.NHC_6H_5 + HCl$$

Diazoamido-benzene.

The resulting substance on standing in presence of an acid undergoes intramolecular change and becomes *p*-amidoazo-benzene, the simplest representative of the azo dyes.

$$C_6H_5.N:N.NHC_6H_5 \rightarrow C_6H_5.N:N-C_6H_4-NH_2$$

p-amidoazo-benzene.

B. The ease with which the sulphonic acids are produced distinguishes the aromatic hydrocarbons from the aliphatic. These substances are readily obtained by heating the former with concentrated or fuming sulphuric; it has not been found possible by this means to introduce more than three of these sulpho groups.

$$C_6H_5.H + OH.SO_2OH = C_6H_5SO_2OH + H_2O$$

Benzene sulphonic acid.

The resulting derivatives or their sodium salts possess a high degree of solubility in water, and consequently the introduction of the sulpho group is of the greatest value when such a property is desirable, as, for instance, in many of the organic dyes.

The two following reactions are characteristic of the sulphonic acids.

i. When fused with potash, phenols are formed, a reaction used in the technical preparation of resorcinol and other phenols.

$$C_6H_5.SO_2OK + K.OH = C_6H_5OH + K_2SO_3$$

ii. Distilled with potassium cyanide the nitriles are formed.

$$C_6H_5SO_2OK + KCN = C_6H_5CN + K_2SO_3$$

C. The third method used for the preparation of the aromatic derivatives depends upon the characteristic behaviour of the benzene homologues on oxidation. Toluene, $C_6H_5CH_3$, for instance, gives benzoic acid, C_6H_5COOH, and, generally speaking, on oxidation the side-chains are replaced by carboxyl groups, whilst the nucleus remains untouched. As previously mentioned, many of the homologues are found in coal-tar, or may be synthesized by the reactions described; the most important of these syntheses was originated by MM. Friedel and Crafts. When the alkyl derivatives of the aliphatic hydrocarbons, preferably the chlorides, are dissolved in benzene and treated with aluminium chloride, hydrochloric acid is evolved and the aliphatic radical is linked on to the benzene nucleus, e. g.

(i) $$CH_3Cl + HC_6H_5 = HCl + C_6H_5CH_3$$

or $$6CH_3Cl + C_6H_6 = 6HCl + C_6(CH_3)_6$$

Hexamethyl benzene.

or (ii) $$CHCl_3 + 3HC_6H_5 = 3HCl + CH(C_6H_5)_3$$

Triphenyl methane.

or (iii) $$C_6H_5.CH_2Cl + HC_6H_5 = HCl + C_6H_5.CH_2.C_6H_5$$

Diphenyl methane.

A similar reaction also takes place between benzoyl chloride and benzene with the formation of diphenyl ketone.

(iv) $$C_6H_5COCl + HC_6H_5 = HCl + C_6H_5.CO.C_6H_5$$

Diphenyl ketone or Benzophenone.

and between carbonyl chloride and benzene with formation of benzoyl chloride.

(v) $$C_6H_5H + ClCOCl = C_6H_5COCl + HCl$$

The reaction is of very considerable importance, but will only take place provided the chlorine atom is attached to aliphatic residues or in the side-chain of a benzene derivative, such, for instance, as (iii) or (iv) above. Phenyl chloride, C_6H_5Cl, for example, cannot replace methyl chloride in reaction (i). The part played by aluminium chloride probably consists in the formation of double compounds such as $C_6H_5Al_2Cl_5$, which with methyl chloride, for instance, regenerate Al_2Cl_6 and give toluene, $C_6H_5.CH_3$. But besides bringing about

synthesis of this type, aluminium chloride can also, under suitable conditions, cause the breakdown of the benzene homologue into benzene; thus if hexamethyl benzene, $C_6(CH_3)_6$, is treated with this reagent and a current of hydrochloric acid conducted through the liquid the methyl groups are broken off as methyl chloride, and $C_6H(CH_3)_5$, then $C_6H_2(CH_3)_4$, &c., and finally benzene itself results.

The oxidation of toluene gives rise to benzoic acid, C_6H_5COOH, and when this substance is acted upon by phosphorus pentachloride, benzoyl chloride, C_6H_5COCl, is formed. The reactivity of this substance may be compared to that of acetyl chloride, previously described, and it is employed for very similar purposes, that is, to introduce the benzoyl group $(C_6H_5CO)'$ into a variety of compounds, e.g.

(i) $C_6H_5NH\overset{\cdots}{H} + C_6H_5CO\overset{\cdots}{Cl} = HCl + C_6H_5NH(COC_6H_5)$
Benzanilide.

(ii) $C_6H_5N(CH_3)\overset{\cdots}{H} + C_6H_5CO\overset{\cdots}{Cl} = HCl + C_6H_5N\begin{matrix}CH_3\\COC_6H_5\end{matrix}$
Methyl-benzanilide.

(iii) $C_6H_5O\overset{\cdots}{H} + C_6H_5CO\overset{\cdots}{Cl} = HCl + C_6H_5COOC_6H_5$
Phenyl-benzoate.

The benzene derivatives can belong to two distinct types, firstly, those in which the hydrogen of the benzene nucleus is substituted. These are obtained by the general methods described, and show the properties of the true aromatic derivatives. The second class is produced by the substitution of the hydrogen atom or atoms in the side-chain, that is, in the aliphatic portion of the molecule; these are obtained by similar methods to those described in the preparation of the paraffin derivatives, and, like these, have corresponding properties. If toluene is taken as an example; when chlorinated at a high temperature benzyl chloride, $C_6H_5CH_2Cl$, is obtained, but if this process takes place in the cold, chlortoluene

$$C_6H_4\begin{matrix}CH_3\\Cl\end{matrix}$$

results. These two substances are of course isomeric, but the first shows the properties of the aliphatic halogen derivatives, the second those of the aromatic.

Benzyl chloride gives the following reactions :—

i. With silver hydrate it gives the corresponding alcohol,

$$C_6H_5CH_2\overset{\cdots}{Cl} + Ag\overset{\cdots}{O}H = C_6H_5CH_2OH + AgCl$$
Benzyl alcohol.

and the alcohol behaves on oxidation in a precisely similar manner to ethyl alcohol,

$$C_6H_5CH_2OH \rightarrow \underset{\text{Benzaldehyde.}}{C_6H_5CHO} \rightarrow \underset{\text{Benzoic acid.}}{C_6H_5COOH}$$

ii. With potassium cyanide benzyl cyanide is formed.

$$C_6H_5CH_2Cl + KCN = KCN + C_6H_5CH_2CN$$

This nitrile further behaves like ethyl nitrile, and on saponification gives the corresponding acid, phenyl acetic, $C_6H_5CH_2.COOH$, and on reduction the amine $C_6H_5CH_2.CH_2NH_2$.

iii. On treatment with ammonia or primary and secondary amines the corresponding substituted amines result,

$$C_6H_5CH_2Cl + HNH_2 = C_6H_5CH_2NH_2 + HCl$$

or $$C_6H_5CH_2Cl + HNHC_6H_5 = C_6H_5CH_2NHC_6H_5 + HCl.$$

Now none of the above reactions take place with chlortoluene,

$$C_6H_4\begin{cases}Cl\\CH_3\end{cases}$$

When the chlorine atom, or, generally speaking, the halogen, is attached directly to the nucleus it is so tightly held that the reactions which are employed in the formation of derivatives of the open-chain hydrocarbons are no longer available for the preparation of the corresponding benzene derivatives. Chlortoluene on oxidation gives chlorobenzoic acid

$$C_6H_4\begin{cases}Cl\\COOH\end{cases}$$

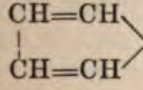
and this substance can pass through a number of changes, in all of which the chlorine atom remains attached to the nucleus. It is only when the so-called negative characteristics of the benzene ring have been depressed, as, for instance, by the introduction of nitro groups, that the reactivity of the chlorine atom appears. So much so may this be the case that in picryl chloride, $C_6H_2(NO_2)_3Cl$, for instance, where there is an accumulation of three such groups, the chlorine shows much about the same power of taking part in reactions as the very reactive benzoyl chloride previously alluded to.

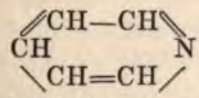
B. GENERAL PHYSIOLOGICAL CHARACTERISTICS OF THE HYDROCARBONS.

The aliphatic hydrocarbons are on the whole less active physiologically than those of the aromatic series. The lower members of the marsh-gas series produce sleep, and, if inhaled, eventually cause death by asphyxia. The toxic properties of this series increase as the carbon atoms become more numerous. Hexane is actively intoxicant, producing a long stage of excitement, followed by deep anaesthesia. Octane, which is contained in the commercial ligroine and in crude petroleum, produces a similar anaesthesia; in addition, there is a tendency to vomiting (Versmann). The unsaturated hydrocarbons, ethylene, propylene, and butylene have very similar action; amylene has properties resembling those of chloroform, but is not so safe. Acetylene (one per cent. in air) produces narcosis with failure of heart and respiration. Lauder Brunton has pointed out that the characteristic action of these aliphatic hydrocarbons is on the nerve centres, tending to produce at first excitement and then narcosis; they act on the sensory side; the aromatic hydrocarbons, on the other hand, act mainly on the motor side, producing convulsions and paralysis.[1] Benzene gives rise to slight paresis of the voluntary muscles, but its principal action is on the higher cerebral centres, producing lethargy and somnolence. Later, a kind of 'intention tremor' occurs in the voluntary muscles. Diphenyl, $C_6H_5 . C_6H_5$, however, is practically inert, and this remarkable diminution in physiological activity extends to many of its compounds.

Naphthalene, which is less toxic than benzene, slows the respiration; small doses raise the blood pressure, whereas large doses depress it. It decreases nitrogenous metabolism, and has an antipyretic action; it has more narcotic action than phenol.

The hetero-cyclic compounds pyrrol, furfurane, and thiophene to a certain extent resemble benzene in their physiological action.

Pyrrol  is more toxic than

Pyridine  and

[1] The solid or liquid nonvolatile hydrocarbons are without physiological action, and pass through the body unaltered. Hence the uselessness of petroleum emulsion as a food-stuff or as a drug.

Piperidine $CH_2\langle\begin{matrix}CH_2—CH_2\\CH_2—CH_2\end{matrix}\rangle NH$ far more so than pyridine.

The physiological reaction of these reduced derivatives decreases with the size of the chain, thus pyrollidine

$$\begin{matrix}CH_2—CH_2\\|\quad\quad\rangle NH\\CH_2—CH_2\end{matrix}$$

is less active than piperidine.

The various substitution products of the hydrocarbons will be dealt with in the subsequent chapters, but some general remarks on alkyl groups, as they affect physiological action, may conveniently be made here.

i. The physiological action of an aliphatic carbon system is generally increased by the entrance of alkyl groups; this is also observed in the aromatic series when the magnitude of the side-chain is increased by the addition of such groups. But with the increase in molecular weight there generally follows a decrease in solubility, volatility, &c., and consequently there comes a period in an homologous series when physiological reactivity begins to decrease owing to lessened absorption by the organism. This is illustrated in the case of the simple alcohols, where the lower members show increasing reactivity as the series is ascended, whereas the higher members are quite inert substances.

ii. In the cyclic compounds the replacement of the hydrogen atoms of the ring by alkyl groups causes a considerable change in physiological action, not always, however, in the same direction. In the case of benzene, toluene, xylene and mesitylene the effect of increasing the number of methyl groups is to cause a diminution of activity, and to some extent a qualitative modification.

In aniline and thiophene, on the other hand, considerably increased toxicity results from substituting the hydrogen of the nucleus by alkyl groups; in phenol the antiseptic power is increased, whilst the toxic action is diminished by such substitution, as in

1 : 3-Cresol . $C_6H_4\langle\begin{matrix}OH\\CH_3\end{matrix}$

iii. In the pyridine homologues the intensity of the action is increased by the entrance of alkyl groups. Pyridine has the least physiological action; picoline (methyl pyridine) is stronger, dimethyl pyridine more so, whereas collidine (trimethyl pyridine) is about six times, and parvuline (tetramethyl pyridine) nearly eight times as

powerful as the parent substance. The entrance of the alkyl group does not lead to a change in the degree of their activity as drugs, but alters their specific effect so that the physiological reaction of the resulting derivatives resembles that of the natural alkaloids.

iv. The replacement of the hydroxyl hydrogen atom in the alcohols is followed by a very considerable rise in volatility and an increase of stability towards oxidizing agents. The hypnotic ethyl alcohol, C_2H_5OH, for example, passes to the anaesthetic substance ether, $C_2H_5.O.C_2H_5$. The inert glycerol becomes the narcotic glycerin-ether

$$\begin{array}{l} CH_2—O—CH_2 \\ | \qquad\quad | \\ CH—O—CH \\ | \qquad\quad | \\ CH_2—O—CH_2 \end{array}$$

In the aromatic series the antiseptic phenol, C_6H_5OH becomes the inert phenetol, $C_6H_5OC_2H_5$. In pyrocatechin

$$C_6H_4\begin{matrix}OH\\OH\end{matrix} \quad 1:2$$

the replacement of one or both of the phenolic hydrogen atoms results in substances of less toxic nature. But on the other hand a similar replacement in the case of resorcin

$$C_6H_4(OH)_2 \; 1:3 \text{ giving } 1:3 \; C_6H_4\begin{matrix}OCH_3\\OCH_3\end{matrix}$$

results in an increase of toxicity.

In the case of 1 : 4-amido-phenol

$$C_6H_4\begin{matrix}OH\\NH_2\end{matrix}$$

a decrease in toxicity follows the replacement of the phenolic hydrogen by either the methyl or ethyl radical.

v. If the hydrogen atoms in ammonia are successively replaced by alkyl groups, the resulting primary, secondary, and tertiary amines show diminishing physiological reaction, the special convulsant effect of ammonia being lost. But as the tertiary amines pass over to the ammonium compounds a great increase in toxicity occurs, and they approach in their action many of the alkaloids.

When the hydrogen atoms of the NH_2 group in aniline are replaced by alkyl groups the physiological action of the resulting substances corresponds to that of the aliphatic amines, and the convulsant action is depressed. But, on the other hand, as previously

remarked, the introduction of alkyls into the nucleus of aniline increases its convulsant action.

The narcotic amides of the aromatic series, such as benzamide, $C_6H_5CONH_2$, and salicylamide,

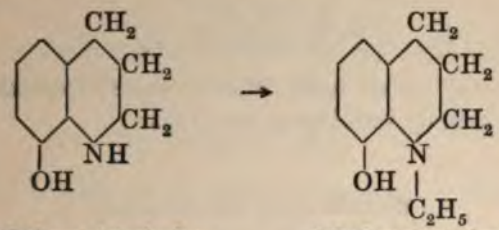
$$C_6H_4\begin{matrix}OH\\CONH_2\end{matrix}\ 1:2$$

lose this action on the replacement of the amido hydrogen atoms, and the resulting substances in large doses are convulsants, like ammonia and strychnine.

vi. The imido hydrogens in xanthine may be substituted by methyl, and the resulting compounds, mono-, di-, and tri-methyl-xanthine show a physiological reactivity which varies considerably from that of the parent substance. The most striking difference is in the action on the cardiac muscle, which develops in proportion to the number of methyl groups.

vii. It is of course only to be expected that in those cases where the replacement of a hydrogen atom by alkyl groups entirely alters the chemical nature of the resulting substance, that a corresponding change in physiological characteristics will appear. For example, the replacement of the carboxylic hydrogen of the organic acids leads to the production of bodies entirely without acid properties (esters), and with altered physiological action; thus the toxic oxalic acid gives rise to the narcotic diethyl oxalate. Similarly salicylic acid gives the less toxic methyl ester (oil of wintergreen). The change produced in the acidic or toxic substance phenol on conversion into its inert ethers has been previously mentioned. On the other hand, physiological activity, which had been hindered by the presence of the carboxyl radical, may again be brought out by the replacement of the hydrogen atom, as is seen in the case of cocaine. Somewhat similar is the alteration produced in the chemically reactive imido derivatives by substitution of the hydrogen atom, resulting in the formation of more stable substances. This may cause the appearance of physiological properties which are absent in the parent substance; thus 1-phenyl-3-methyl pyrazolon (p. 204), containing an NH group, is entirely wanting in the characteristic antipyretic properties of antipyrine, which contains an $N.CH_3$ group; or it may result in a decrease of toxicity, as in case of 1-hydroxy-tetra-hydro quinoline; this subst[illegible]s methyl ester) possesses marked antipyretic properties, [illegible]oplasmic poison, and hence cannot be used as a drug.

Fischer and Filehne ascribed the toxic secondary effects to the presence of the reactive imido group, and they found, as expected, that on converting this into 1-hydroxy-tetrahydro-*n*-ethylquinoline, and so increasing the stability, they obtained a derivative with far less toxic action, introduced into pharmacy in 1883 under the name of *Kairine.*



1-Hydroxy-tetrahydro-quinoline.

1-Hydroxy-tetrahydro-*n*-ethylquinoline (*kairine*).

Differences between the Methyl and Ethyl Groups.

The ethyl group appears to have a certain affinity for the central nervous system, as many substances containing this radical have pronounced hypnotic properties which are entirely wanting in the corresponding methyl derivatives. This is strikingly shown in the group of sulphones, whose hypnotic properties appear to be solely determined by the presence of the ethyl group, since the methyl derivatives are quite inert. 1 : 2-amidophenol has no hypnotic properties, but when the hydrogen atom of either the hydroxyl or the amido group is replaced by methyl, derivatives with slight narcotic power result, thus

$$C_6H_4\begin{matrix}OCH_3\\NH.CH_3\end{matrix}\ 1:2$$

and

$$C_6H_4\begin{matrix}OCH_3\\N(CH_3)_2\end{matrix}$$

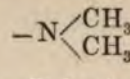
have slight narcotic properties, but the triethyl derivative on the other hand

$$C_6H_4\begin{matrix}OC_2H_5\\N(C_2H_5)_2\end{matrix}$$

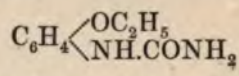
has pronounced action. In this connexion it is interesting to note Ehrlich and Michaelis's observation that certain dyes containing an amido group in which both hydrogen atoms have been replaced by ethyl, thus

$$-N\begin{matrix}C_2H_5\\C_2H_5\end{matrix}$$

are capable of staining nerve structure, whereas the corresponding dimethyl compounds



do not possess this property. It has been observed that dulcin



has an extremely sweet taste, whereas the corresponding methyl derivative is entirely wanting in this property.

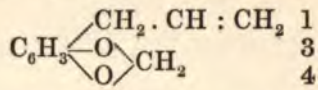
Unsaturated Substances.

An important factor in the physiological action of organic substances is the presence in the molecule of unsaturated or doubly unsaturated carbon systems. The apparently low valency shown by carbon in various series of compounds has previously been discussed, and the difference in the significance of the double bond in open and closed chain derivatives described (pp. 26, 28).

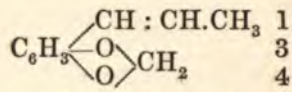
Generally speaking, open-chain derivatives containing unsaturated carbon atoms are more toxic than the corresponding saturated bodies. Thus allyl alcohol, $CH_2:CH.CH_2OH$, is fifty times more toxic than *n*-propyl alcohol, $CH_3.CH_2.CH_2OH$. Acrolein, $CH:CH.COH$, and croton-aldehyde, $CH_3.CH:CH.COH$, are more toxic than the corresponding saturated aldehydes.

On the other hand, allylamine, $CH_2:CH.CH_2NH_2$, is without physiological action, but vinylamine, $CH_3.CH:CHNH_2$, is very toxic. Generally speaking, the group $(C:CH.NH_2)''$ appears to be especially active in this respect.

With these examples may be compared safrol



the most toxic of all the etherial oils, and the much less poisonous isosafrol



The doubly unsaturated di-iodo-acetylene, $CI:CI$, is stated to be one of the most toxic bodies known.

Choline

$$(CH_3)_3 : N\begin{cases} CH_2 \cdot CH_2OH \\ OH \end{cases}$$

is but slightly toxic, whereas its dehydration product neurine

$$(CH_3)_3 : N\begin{cases} CH : CH_2 \\ OH \end{cases}$$

is extremely toxic, and this characteristic is still more pronounced in the doubly unsaturated compound

$$(CH_3)_3 : N\begin{cases} C : CH \\ OH \end{cases}$$

On the other hand, allyl-trimethyl ammonium hydrate

$$(CH_3)_3 : N\begin{cases} CH_2 \cdot CH : CH_2 \\ OH \end{cases}$$

a homologue of neurine, is only slightly toxic. This substance is a derivative of the physiologically inactive allyl-amine

$$H_2N.CH_2 \cdot CH : CH_2.$$

Numerous other instances occur, but need not be quoted. Sufficient examples have been given to show that though as a rule the unsaturated compounds are more toxic than the saturated, yet this is not invariably the case. To the exceptions already mentioned may be added the inert cinnamic, $C_6H_5CH : CH.COOH$, and aconitic acids

$$\begin{array}{l} CH.COOH \\ \| \\ C.COOH \\ | \\ CH_2 \cdot COOH. \end{array}$$

It is however highly probable that in both these cases the presence of the carboxyl group has been sufficient to depress physiological reactivity.

Isomerism.

The structural arrangement of the atoms in the molecules of isomeric bodies plays such an important part in their physiological action, and is described in such detail throughout this work, that only a few points will be mentioned here.

As typical of the interdependence of physiological action and molecular structure among the aliphatic series such compounds as

the primary and secondary alcohols may be compared. Here the isomeric secondary have greater narcotic and toxic characteristics than the primary alcohols. The differing toxicity of allylamine and its isomer vinylamine has already been mentioned. In the aromatic series the isomeric ortho, meta, and para substitution products often vary considerably in their therapeutic or toxic capacity, but there is no general rule as to which of the three will be more and which least active.

Bokorny found that 1 : 4 compounds were generally more toxic for the lower plants and animals, thus

1 : 4-nitrophenol, $C_6H_4\langle^{OH}_{NO_2}$, 1 : 4-nitrotoluene, $C_6H_4\langle^{NO_2}_{CH_3}$,

1 : 4-bromtoluene, $C_6H_4\langle^{NO_2}_{Br}$

are all more toxic than their isomeric 1 : 2 or 1 : 3 derivatives. On the other hand, 1 : 2-nitrobenzaldehyde is more toxic than the 1 : 4 derivative, and salicylic acid

$$C_6H_4\langle^{OH}_{COOH}\ 1:2$$

is the only one of the three isomeric oxybenzoic acids which is therapeutically active.

Gibbs showed that the toxic dose per kilo weight of the dioxybenzenes was

·06 gm. in the case of 1 : 2 $C_6H_4\langle^{OH}_{OH}$, ·1 gm. with 1 : 4 $C_6H_4\langle^{OH}_{OH}$,

and in the case of resorcin, 1 : 3' $C_6H_4\langle^{OH}_{OH}$, 1·0 gm.

The three isomeric amido-toluenes showed very similar physiological action. Injected into the jugular vein of a dog the following amounts represented the toxic doses per kilo weight:

1 : 2-toluidine, $C_6H_4\langle^{CH_3}_{NH_2}$ = ·208 gm.,

1 : 3 = ·125 gm., 1 : 4 = ·10 gm.

Occasionally, unlike the preceding case of the toluidines, there is an alteration in specific action dependent on the relative position of the substituting groups in benzene. The three cresols

$$C_6H_4\langle^{OH}_{CH_3}$$

are an example of this. They stimulate the vagus centre, causing heart failure, and also act peripherally on the nerve endings and

are vasomotor poisons. All three cresols act equally on the peripheral nerve endings, but ortho- and para-cresol, especially the former, are much more powerful vagus stimulants, whereas ortho- and meta-cresol act more markedly on the vasomotor system. Numerous other instances will be found in the subsequent chapters.

Stereochemical relationships.

Pasteur in 1860 described the connexion between chemical configuration of molecules and their action on ferments, and showed that while certain moulds were capable of breaking down *dextro*-rotatory tartaric acid, they had no action on the *laevo*-rotatory acid. Emil Fischer described many sugars which react towards ferments in a similar manner, one optical isomer being attacked by an enzyme, the other not. He thought that the explanation of the phenomenon 'probably lies in the structure of the enzyme . . . for doubtless the enzymes are optically active and consequently possess an asymmetric structure'. This led to the view that the molecular configuration of the enzyme and of the fermentable sugar are complementary, so that 'the one may be said to fit the other as a key fits a lock'. But it must be remembered that we are in a state of profound ignorance as to the configuration of the enzymes. As regards the animal organism, Brion found that *laevo*- and *meso*-tartaric acids were oxidized to an almost equal extent and that *dextro*-tartaric was attacked to a much less extent than either, whereas racemic acid was least oxidized of all these stereochemical isomers.

These examples are sufficient to indicate that there is an unquestionable interdependence between the stereochemical configuration of the molecule and physiological action.

That the configuration of the molecule has an influence upon the sense of taste is illustrated in the case of *dextro*-asparagine, which is sweet, whilst the *laevo*-rotatory modification is not; *dextro*-glutaminic acid is sweet, whereas the *laevo* acid is tasteless.

The influence of configuration on the toxicity of isomers has been observed in some cases, thus the local anaesthetic action of *dextro*-cocaine on the tongue is stronger and sets in more rapidly than that of the *laevo* modification, although the effect is not so lasting. Mayor states that *laevo*-nicotine is twice as toxic as the *dextro* derivative. Atropine has a more powerful stimulating action on the spinal centres than hyoscyamine. But one of the most interesting observations was that made originally by Crum

Brown and Fraser, who showed that many alkaloids, when acted upon by alkyl iodides, gained a curare-like action (paralysis of ends of motor nerves of muscles) without losing their individual characteristics. In all these cases the conversion of nitrogen from the tri- to the quinquevalent condition occurs (see pp. 2 and 20). That this new characteristic is dependent on the space relations of the molecule is clearly shown by the investigation of analogous substances, and of changes in bodies not containing nitrogen. Thus it has been shown that phosphorus, arsenic, and antimony derivatives lose their physiological characteristics on being converted, by the action of alkyl iodides, into salts of the phosphonium, arsonium, and stibonium bases, which possess strong curare-like action. This clearly indicates that the change in physiological action is not merely dependent on the passage of trivalent atoms to quinquevalent, but rather on the change in stereochemical configuration;—on a change from a plane to a tridimensional arrangement of the atoms. This is still more clearly shown in Curci and Kunkel's observation that the change of the inert dimethyl-sulphide, $(CH_3)_2S$, to trimethyl-sulphine-hydroxide, $(CH_3)_3S.OH$, also results in the appearance of the curare character. Now, in the case of sulphur, a divalent element, the configuration of the sulphide must be plane, but with the appearance of two extra valencies in the second derivative the configuration changes to the solid, as shown by the fact that such substances may exist in optically active forms.

CHAPTER III

CHANGES IN ORGANIC SUBSTANCES PRODUCED BY METABOLIC PROCESSES

Syntheses — Sulphuric and Glycuronic acid derivatives, Compounds of Amidoacetic acid, Urea. Sulphocyanides. Introduction of Acetyl and Methyl radicals. Cystein derivatives. Processes of Oxidation and Reduction.

The investigations which have been made on the changes produced in organic substances by their passage through the organism have led to the generalization that such changes always tend to the formation of less toxic bodies. From the point of view of the synthetic preparation of drugs, it is most important to observe that these modifications generally lead to the production of derivatives with more acidic properties—or, in other words, the introduction of acid groups tends to lower the toxicity of an organic substance.

If the course of a drug through the system is followed, it is found that no reaction takes place in the mouth, but in the stomach the hydrochloric acid present may cause an increase in the solubility of basic substances, and also cause the breakdown of such derivatives as the anilides into aromatic amines and acids, and the absorption of basic substances will consequently start from this region. The pepsin present has little if any action. In the intestines the alkali present may cause an increase in the solubility of organic acids, or the decomposition of their metallic salts, but a much more important action is that of the pancreatic juice and bile which bring about the saponification, not only of the fats, but of such esters as salol, giving phenol and salicylic acid. Nencki was the first to realize the value of this fact, and his so-called 'salol principle', founded upon this, will be described in detail later on.

But it is in the tissues or blood that the more profound changes of oxidation and reduction take place. Besides these two main alterations, various synthetic processes are also carried out, all tending, as previously mentioned, towards a reduction in the toxicity

of the original substance. The latter processes will be described first, though it generally happens that they follow those of oxidation or reduction before the final elimination of the substance in the urine.

A. SYNTHETIC PROCESSES.

Of these the most important that take place are with sulphuric and glycuronic acids or amidoacetic acid. Next in importance is the formation of urea derivatives and sulphocyanides, and, less seldom met with, the introduction of acetyl or methyl groups and the production of cystein derivatives. Although this does not exhaust the various reactions which have been described, it includes all the more important, and in the discussion of these only a few typical examples of each will be given.

It does not often happen that a particular substance is excreted entirely in any one form, as for instance as a sulphonic ester; it may be found chiefly in that form, but also partially as a glycuronic acid derivative, or even partially unchanged, this may depend on dosage or other factors quite unknown. Consequently, in the various reactions discussed, it must be understood that the elimination of the substance in question chiefly occurs by means of the synthesis under which it is described, but that at the same time others may take place, which, judging from the relative amounts in the urine, are of lesser importance.

I. Sulphonic Esters.

The sulphuric acid required for the production of these substances must be formed by the oxidation of albuminous bodies containing sulphur, and in this connexion it may be mentioned that etherial hydrogen sulphates in the urine are generally increased in conditions interfering with the normal performance of the hepatic functions. The etherial sulphates normally found in the urine represent only one-thirteenth of the total sulphates. Though partially derived from tissues, the greater part are due to protein decomposition in the intestine, hence their increase in conditions of intestinal putrefaction and obstruction. When decomposition of protein matter within the organism is taking place on a large scale, as e. g. in foul empyemata, or gangrene of internal organs, a similar increase in etherial sulphates in the urine is noted.

Indican (indoxyl potassium sulphate), which occurs in small amounts in normal urine, is increased under like conditions.

Aromatic substances containing hydroxyl, (OH), in the nucleus are generally found combined with sulphuric acid as alkali salts in the urine, synthesis with glycuronic acid also taking place.

Phenol, $C_6H_5.OH$, for instance (besides undergoing further oxidation to dioxybenzenes), is found as phenyl sulphuric acid, the following reaction taking place :—

$$C_6H_5O\!:\!H + OH\!:\!SO_2.OH = H_2O + C_6H_5.O.SO_2.OH.$$

The free acid itself is unknown, since on liberation from its salts by strong hydrochloric acid, it immediately breaks down into sulphuric acid and phenol. Such substances, although stable in aqueous or alkaline solutions, are readily decomposed by mineral acids.

The toxicity of phenol has consequently been diminished by this synthesis, and it was only to be expected that sodium or potassium phenyl sulphate should be non-toxic substances. Further than this the introduction of the sulphonic acid grouping into the ring itself, giving rise to phenol sulphonic acid

$$C_6H_4\begin{cases}OH\\SO_2OH\end{cases}$$

produces a substance which is equally innocuous.

If the hydroxyl derivative itself is non-toxic, owing to the presence of some grouping in the ring, then it passes unchanged through the organism; an example of this is homogentisinic acid

$$C_6H_3\begin{cases}OH & 1\\OH & 4\\CH_2.COOH & 5\end{cases}$$

whereas the corresponding gentisinic acid,

$$C_6H_3\begin{cases}OH & 1\\OH & 4\\COOH & 5\end{cases}$$

which is toxic, is partially eliminated as the non-toxic sulphuric acid derivative. Similarly the highly poisonous hydroquinone

$$C_6H_4\begin{cases}OH\\OH\end{cases}\ 1:4$$

leaves the system in the form of its sulphonic ester.

Many of the aromatic ketones are oxidized to acids in the body, but when they contain a hydroxyl group, and the possibility of combination with sulphuric or glycuronic acids appears, then these

latter syntheses take place to the exclusion of the former. Acetophenone, $C_6H_5.CO.CH_3$, for instance, is oxidized to benzoic acid, C_6H_5COOH, but

Paeonol $C_6H_3\begin{cases}OH & 1\\ CO.CH_3 & 2\\ O.CH_3 & 5\end{cases}$

Gallacetophenone $C_6H_2\begin{cases}OH & 1\\ OH & 2\\ OH & 3\\ CO.CH_3 & 4\end{cases}$

and Resacetophenone $C_6H_3\begin{cases}OH & 1\\ OH & 3\\ CO.CH_3 & 4\end{cases}$

are found in the urine as their sulphuric and glycuronic acid derivatives.

The entrance of an acid group into the nucleus of the phenols causes the loss of this power of uniting with sulphuric acid, for instance, salicylic acid

$$C_6H_4\begin{cases}OH & 1\\ COOH & 2\end{cases}$$

and also the 1:4 isomer (both much less toxic than phenol) are not eliminated as esters, but behave like benzoic acid. When the acid character is lost, however, either by conversion into an ester such as

$$C_6H_4\begin{cases}OH & 1\\ COO.CH_3 & 2\end{cases}$$

or an amide

$$C_6H_4\begin{cases}OH & 1\\ CO.NH_2 & 2\end{cases}$$

these bodies regain their characteristics and are found as sulphuric derivatives (Baumann and Herter); the introduction of more hydroxyl groups into the ring causes the reappearance of this synthesis, as in the previously mentioned case of gentisinic acid or protocatechuic acid,

$$C_6H_3\begin{cases}COOH & 1\\ OH & 3\\ OH & 4\end{cases}$$

also vanillic acid,

$$C_6H_3\begin{cases}COOH & 1\\ OCH_3 & 3\\ OH & 4\end{cases}$$

and isovanillic—

$$C_6H_3\begin{cases}COOH & 1\\ OH & 3\\ OCH_3 & 4\end{cases}$$

But veratric acid

$$C_6H_3\begin{cases}COOH & 1\\ O.CH_3 & 3\\ O.CH_3 & 4\end{cases}$$

passes through the body unchanged, since it contains no free hydroxyl groups, and consequently cannot undergo the sulphuric or glycuronic acid syntheses. In this connexion it may be pointed out that a methoxy group $(O.CH_3)'$, replacing hydrogen of the benzene nucleus, is much more resistant towards the oxidizing influences of the body than is a similarly situated methyl group (see p. 76).

II. Glycuronic Acid Derivatives.

Glycuronic acid, $COH\,(CH.OH)_4COOH$, may be obtained by the reduction of saccharic acid, $COOH.(CH.OH)_4.COOH$, and is a syrup which rapidly passes into its lactone on warming; nothing certain is known of its origin in the body.

Glycuronic acid appears in the urine in poisoning by

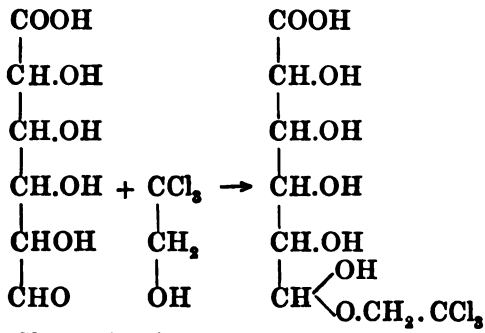
Phosphoric acid.	Antipyrin.
Phosphorus.	Pyramidon.
Lactic acid.	β-naphthol.
Hydrochloric acid.	Sandal-wood oil.
Strychnine.	Chinosol.
Curare.	Chloral hydrate.
Arsenic.	Resorcin.
Butyl chloral hydrate.	Acetanilide.
Morphine.	Phenetidin.
Prussic acid.	Menthol.
Chloroform.	Borneol.
Turpentine.	Camphor.

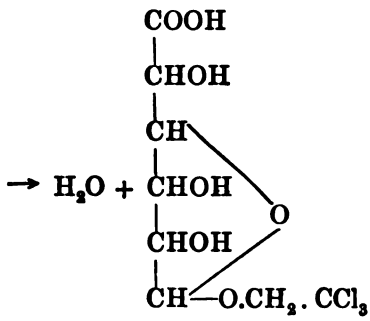
It is usually found in diabetic urine, and is thought by some to be a preliminary derivative of sugar, the oxidation of which is in that disease carried so far and no further.

In the various syntheses which take place in the animal organism it is probable that combination with grape sugar takes place first,

and then the primary alcohol group present is oxidized, with the result that glycuronic acid derivatives finally appear. As regards the nature of the resulting compounds, they appear to be (at all events in the case of aliphatic substances), very analogous to the glucosides. Taking chloral as an example, it is found that it is reduced in the body and eliminated as urochloralic acid, a synthesis which may probably be represented by the scheme

1. $CCl_3.CHO + H_2 = CCl_3.CH_2.OH$
Chloral. Trichlorethyl alcohol.

2.

Glycuronic acid.


Urochloralic acid.

It appears, however, that a different type of combination can take place; thus Y. Kotake[1] has shown that rabbits dosed with vanillin eliminate in the urine a glycuronic acid derivative of vanillic acid, the first reaction consisting in the oxidation of the aldehyde, which

[1] *Zeit. f. physiol. Chem.*, 45, 320.

then condenses with glycuronic acid without the elimination of water,

1. $C_6H_3\begin{cases}CHO & 1\\ O.CH_3 & 3\\ OH & 4\end{cases}$ Vanillin. $C_6H_3\begin{cases}COOH & 1\\ O.CH_3 & 3\\ OH & 4\end{cases}$ Vanillic acid.

2. $$\begin{matrix}COOH\\ |\\ (CHOH)_4\\ |\\ CHO\end{matrix} + C_6H_3\begin{cases}COOH\\ O.CH_3\\ OH\end{cases} = \begin{matrix}COOH\\ |\\ (CHOH)_4\\ |\\ CH\end{matrix}\!\!<\begin{matrix}OH\\ O.C_6H_3\end{matrix}\!\!\begin{cases}COOH\\ O.CH_3\end{cases}$$

Blum has shown that thymol behaves in a similar manner,

$$C_3H_7.CH_3.C_6H_3OH + C_6H_{10}O_7 = C_3H_7.CH_3.C_6H_3O.C_6H_{11}O_7$$

and Fenivessy that carbostyril also unites with glycuronic acid without the elimination of water,

$$(C_6H_4)C_3H_2N.OH + C_6H_{10}O_7 = (C_6H_2).C_3H_2N.O.C_6H_{11}O_7.$$

There does not seem to be any sharp line of demarcation drawn between these two groups by any of the investigators of these glycuronic derivatives. In but relatively few cases have they been isolated in a state of purity, the statement usually met with being that such and such a substance is eliminated conjugated with glycuronic acid.

It is possible that hydroxy derivatives of the aliphatic series which combine with this acid do so in a similar manner to trichlorethyl-alcohol, i. e. form true glucosides; such are bromal and butyl chloral, which are firstly reduced to the corresponding alcohol; the secondary alcohols and, to a much less extent, the primary (except methyl and ethyl, which are readily oxidized), and also alcohols of high molecular weight; some polyhydric alcohols, such as propylene glycol, but not glycerol[1]; many aliphatic ketones, such as dichloracetone, which are firstly reduced to their secondary alcohols. Acetoacetic ester is firstly oxidized to carbon dioxide and acetone, and this latter reduced to secondary propylalcohol; it is then eliminated as its glycuronic acid derivative. Finally come tertiary alcohols, such as tertiary butyl, tertiary amyl, and pinacone.

On the other hand some aromatic hydroxyl derivatives may form addition products similar to those produced with vanillic acid or

[1] Otto Neubauer, *Chem. Centr.*, 1901, ii. 314, from *Arch. Exp. Path. Pharm.*, 46, 133–54.

thymol, but no definite statement can be made, since condensation with elimination of water is stated to take place in the following cases. Lesnik[1] found that both α- and β-naphthol occurred in the urine as such derivatives

$$C_{10}H_7OH + C_6H_{10}O_7 = C_{10}H_7 . O.C_6H_9O_6 + H_2O.$$

Pellacani[2], confirmed by Bonanni[3], found a similar product in the case of borneol and menthol,

$$C_{10}H_{17}OH + C_6H_{10}O_7 = C_{10}H_{17} . O.C_6H_9O_6 + H_2O$$

and

$$C_{10}H_{19}OH + C_6H_{10}O_7 = C_{10}H_{19}O.C_6H_9O_6 + H_2O.$$

Schmiedeberg and Meyer[4] found that camphor was firstly oxidized to campherol,

$$C_{10}H_{16}O \rightarrow C_{10}H_{15}O.OH$$

and then eliminated as a condensation product with glycuronic acid,

$$C_{10}H_{15}O.OH + C_6H_{10}O_7 = C_{10}H_{15}O.O.C_6H_9O_6 + H_2O.$$

Other investigators have noticed reactions corresponding to the latter in case of carvon, pinene, phellandrene, and sabinene. Salkowski and Neuberg have recently shown that the synthetical phenylglycuronic acid melting at 150°, and of composition

$$C_6H_5O.C_6H_9O_6$$

is identical with the acid excreted in the urine of a sheep dosed with phenol.

An interesting synthesis is that undergone by phenetol,

$$C_6H_5OC_2H_5,$$

which is firstly oxidized and then eliminated with glycuronic acid as the so-called chinaethonic acid,

$$C_6H_5OC_2H_5 \rightarrow 1:4\ C_6H_4\begin{matrix}OH\\OC_2H_5\end{matrix} + C_6H_{10}O_7$$

$$= H_2O + p\text{-}C_6H_4\begin{matrix}O.C_6H_9O_6\\OC_2H_5\end{matrix}$$

Another method by means of which the toxicity of a substance is lowered consists in the addition of water; Fromm and Hildebrandt[5] have shown that thujon is converted in the body to thujonhydrate and then eliminated as a glycuronic derivative,

$$O.C_{10}H_{16} + H_2O = O.C_{10}H_{17}OH$$

and

$$O.C_{10}H_{17}OH + C_6H_{10}O_7 = O.C_{10}H_{17}O.C_6H_9O_6.$$

[1] Schmiedeberg, *Arch.*, 24, 167.
[2] *Arch. f. Exp. Path. u. Pharm.*, 17, 369.
[3] Hoffmeister, *Beitrag z. Chem. Physiol.*, 1, 304.
[4] *Zeit. f. physiol. Chem.*, 3, 422. [5] *Zeit. f. physiol. Chem.*, 33, 579.

III. Derivatives of Amidoacetic acid.

Amidoacetic acid, glycocoll or glycine is the simplest amido acid, and may be obtained synthetically by warming monochloracetic acid with dry ammonium carbonate.

$$COOH.CH_2Cl + HNH_2 = COOH.CH_2.NH_2 + HCl$$

It is soluble in water, possesses a sweet taste, and was shown by Nencki and Schultzens[1] to give rise to urea when administered in food (see p. 74).

The fact that glycine and other amino acids give rise to urea if introduced with food or intravenously, and the fact of their appearance in the urine in acute yellow atrophy of the liver (where urea elimination is decreased correspondingly), are taken as indicating the position of those bodies as intermediaries between protein and urea. This may or may not be true, but if true, some synthesis must precede the formation of urea, as the amino acids contain less N than C, which is the reverse of what occurs in urea.

The combination of glycine and benzoic acid takes place in the kidney substance, at any rate partially. Minced kidney substance can effect this synthesis, and blood containing benzoic acid, if passed through the living kidney, is found afterwards to contain hippuric acid.

This typical synthesis, the first of its kind which was discovered, is illustrated by benzoic acid, which forms hippuric acid,

$$\underset{\text{Amidoacetic acid.}}{CH_2(COOH).NHH} + HO.OC.C_6H_5 = H_2O + \underset{\text{Hippuric acid.}}{CH_2(COOH)—NH.CO.C_6H_5}$$

A similar reaction takes place with any benzene derivative which, if oxidized in the body, gives rise to this acid or its derivatives, such, for instance, as toluene, ethyl or propyl benzene, xylene (firstly oxidized to

$$C_6H_4\begin{cases}CH_3\\COOH\end{cases},$$

mesitylene (firstly oxidized to mesitylenic acid), *p*-nitrotoluene, *p*-bromtoluene, and in the case of dogs all the nitrobenzaldehydes.

Salicylic, *p*-oxybenzoic, nitrobenzoic, chlor and brombenzoic acids, anisic, α- and β-naphthoic, toluic, mesitylenic and cuminic acids all

[1] *Zeit. f. Biol.*, 8, 124, 1872.

form derivatives analogous to hippuric acid. In this connexion it may be mentioned that whereas phenyl propionic acid

$$C_6H_5CH_2.CH_2.COOH$$

is oxidized in the body to benzoic acid and eliminated as hippuric acid, phenyl acetic acid, $C_6H_5CH_2.COOH$, forms phenyl aceturic acid, $C_6H_5CH_2.CO.NH.CH_2COOH$; but this question will be further discussed under the general heading of oxidation processes.

The α-carboxylic acid of thiophene, and the corresponding aldehyde after oxidation in the organism, behave in a similar manner to benzoic acid.

α-methyl pyridine is firstly oxidized to the α-carboxylic acid and then eliminated as a glycocoll derivative.

IV. Urea Derivatives.

The mode of formation of these derivatives is by no means clear; they may be formed outside the body by the action of cyanic acid on primary or secondary amines.

$$\underset{\text{Cyanic acid.}}{C_2H_5.NH_2 + CONH} = \underset{\text{Ethyl urea.}}{C_2H_5.NH.CO.NH_2}$$

and it may be that a reaction somewhat analagous to this takes place in the animal organism.

Taurin

$$\begin{array}{l} CH_2NH_2 \\ | \\ CH_2.SO_2OH \end{array}$$

is eliminated as taurocarbamic acid

$$\begin{array}{l} CH_2.NH.CO.NH_2 \\ | \\ CH_2.SO_2OH \end{array}$$

Amido-benzoic and amido-salicylic acids similarly form urea derivatives,

$$C_6H_4\begin{array}{l}\diagup COOH \\ \diagdown NH.CO.NH_2\end{array} \quad \text{and} \quad C_6H_3\begin{array}{l}\diagup COOH \\ -OH \\ \diagdown NH.CO.NH_2.\end{array}$$

Schmiedeberg noticed small quantities of ethyl urea

$$C_2H_5.NH.CO.NH_2$$

in the urine after dosing with ethylamine carbonate.

Many derivatives appear in the urine as salts of urea. Sieber

and others found that the nitrobenzaldehydes are firstly oxidized to their corresponding acids, then combine with glycocoll to nitrohippuric acids, and that these latter substances then formed salts with urea.

V. Formation of Sulphocyanides.

Pascheles[1] showed that some proteins containing easily split-off sulphur could convert potassium cyanide into sulphocyanide, KCNS, at the temperature of the room, and it is probable that the formation in the animal organism of sulphocyanides from the organic nitriles may be ascribed to a similar reaction. With the exception of methyl nitrile, CH_3CN, the homologues of this series are very poisonous, and in their passage through the body are converted into the much less toxic sulphocyanides. It is interesting to note that Nencki[2] states that the stomach under normal conditions contains a minute amount of free sulphocyanic acid. Gscheidlen found it constantly in human urine, and the potassium salt occurs normally in saliva, probably as an excretory product.

VI. Introduction of the Acetyl Radical.

One of the most interesting examples of the introduction of an acetyl group in the passage of an organic substance through the body was observed by R. Cohn[3], who found that rabbits treated with *m*-nitrobenzaldehyde converted this into *m*-acetylamidobenzoic acid.

The first change consists in the oxidation of the aldehyde group to the acid,

$$C_6H_4\begin{matrix}COH\\NO_2\end{matrix} + O = C_6H_4\begin{matrix}COOH\\NO_2\end{matrix}$$

The second, the reduction of nitrobenzoic acid to amidobenzoic,

$$C_6H_4\begin{matrix}COOH\\NO_2\end{matrix} + 6H = 2H_2O + C_6H_4\begin{matrix}COOH\\NH_2\end{matrix}$$

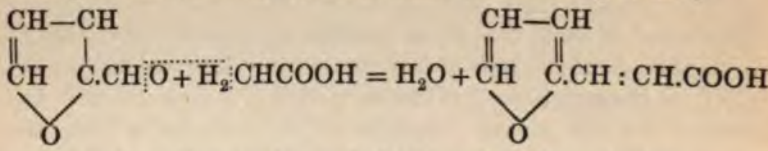
and thirdly, the synthetic formation of the acetyl derivative,

$$C_6H_4\begin{matrix}COOH\\NH\,H\end{matrix} + \begin{matrix}CH_3\\|\\CO\,OH\end{matrix} = C_6H_4\begin{matrix}COOH\\NH.CO.CH_3\end{matrix} + H_2O$$

[1] *Arch. f. exp. Pathol. u. Pharm.*, **34**, 281.
[2] *Ber.*, **28**, 1318.
[3] *Zeit. physiol. Chem.*, **18**, 133-6.

VII. Reactions with Acetic Acid.

Jaffé and Cohn[1] found that furfurol, the aldehyde of furfuran, is partly oxidized in the organism to the corresponding acid, and then eliminated as a glycocoll derivative, but to a smaller extent it undergoes condensation with acetic acid to furfuracrylic acid,

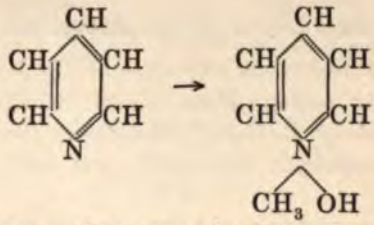


which is then eliminated as a derivative of amidoacetic acid,

$$C_4H_3O.CH:CH.COOH + H_2N.CH_2.COOH = H_2O + C_4H_3O.CH:CH.CO.NH.CH_2COOH$$

VIII. Introduction of the Methyl Radical.

His[2] found that pyridine is eliminated in the urine as methyl-pyridyl-ammonium hydroxide, and this observation was confirmed by R. Cohn[3]; it is one of the most interesting changes in animal chemistry.

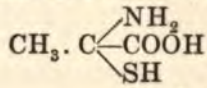


Hoffmeister states that an animal dosed with tellurium or tellurium compounds eliminates tellurium dimethide, $Te(CH_3)_2$.

In this connexion it is interesting to notice that according to the observations of Albanese, Gottlieb, Krüger, and Schmidt the methylated xanthines are deprived of one or more of their methyl groups on passing through the organism.

IX. Formation of Cystin Derivatives.

Baumann showed that cystin, one of the primary dissociation products of proteins, found in urine in cases of cystinuria, is the disulphide of cystein, which he formulated

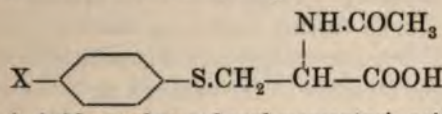


[1] *Ber.*, **20**, 2311. [2] *Archiv exp. Path. Pharm.*, 22.
[3] *Zeit. physiol. Chem.*, **18**, 112-30.

but C. Neuberg and Friedmann proved later that the amido and (SH) groups were attached to different carbon atoms,

$$SH.CH_2 . CH.NH_2COOH.$$

When dogs are treated with either chlor- or brom-benzene the mercapturic acids formed are derived from the same cystein which is found in protein-cystin. In the urine these compounds are combined with a strong laevo-rotatory, monobasic acid, and when decomposed with mineral acids give chlor- or brom-phenyl-mercapturic acid, substances of the following constitution :—



1 : 4-chlor- or brom-phenyl-mercapturic acid.

These may be synthesized by heating brom-phenyl-cystein dissolved in benzene with acetic anhydride.

B. OXIDATION.

By oxidation is meant not only the combination of oxygen with a compound, but also the splitting off of hydrogen, or its replacement by oxygen.

The final oxidation products of carbonaceous compounds are carbon dioxide and water, and if nitrogen is present this may appear in the free state; the term combustion is usually employed to such a complete breakdown.

The change of food-stuffs in the body is very similar; carbon dioxide is the end oxidation product of the carbon, but the nitrogen appears mainly as uric acid or urea.

In organic compounds the introduction of oxygen is almost invariably accompanied by an increase in the velocity of reaction, and the 'inertia' of the carbon complex, previously mentioned, is largely diminished, the more so as the accumulation of oxygen increases.

When once partial oxidation of the hydrocarbon has set in, the further replacement of hydrogen by oxygen becomes easier and easier. Thus methane, CH_4, is only oxidized with considerable difficulty. Methyl alcohol, $CH_3 . OH$, is readily oxidized to formaldehyde, H.COH, and this passes even on exposure to the air to formic acid, H.COOH. Formaldehyde abstracts oxygen from silver oxide, formic acid from the more stable mercuric oxide.

Then in complex compounds containing oxygen further oxidation always takes place at the most highly oxidized place in the molecule, provided the carbon at that point is linked to hydrogen.

Thus ethyl alcohol, $CH_3.CH_2OH$, is oxidized to acetaldehyde, $CH_3.CHO$, and this further to acetic acid, $CH_3.COOH$; and β-oxypropyl aldehyde, $CH_3.CHOH.CH_2.CHO$, is converted into β-oxybutyric acid, $CH_3.CHOH.CH_2.COOH$, since the aldehyde group $(CHO)'$ is the most highly oxidized system in the molecule.

It is a very general rule that a carbon atom cannot be linked to more than one hydroxyl group, and when attempts are made to introduce more, i. e. on further oxidation, water is split off, and the following general reactions take place, depending upon the number of hydrogen atoms attached to the oxidized carbon :—

1. $CH_2OH.CH_2.CH_3$ (Propyl alcohol.) $\xrightarrow{O \text{ (Oxidized.)}}$ $CH(OH)_2.CH_2.CH_3 = H_2O + CHO.CH_2.CH_3$ (Butyric aldehyde.)

or O_2 $\searrow$ $C(OH)_3.CH_2.CH_3 = H_2O + COOH.CH_2.CH_3$ (Butyric acid.)

The aldehydes are consequently the intermediate, and the organic acids the final products in the oxidation of alcohols containing the primary group $X—CH_2OH$. With secondary alcohols, i. e. those containing the

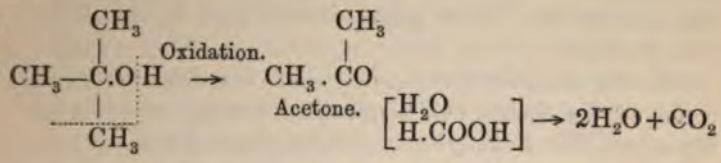
$$\begin{matrix} X \\ X \end{matrix}\!\!>\!CH.OH$$

group, a similar reaction takes place, and on further oxidation they yield ketones,

2. $CH_3.CH(OH).CH_3 \xrightarrow{O} CH_3.C(OH)_2.CH_3 = H_2O + CH_3.CO.CH_3$

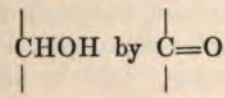
Acetone or dimethyl ketone.

With tertiary alcohols, such as $(CH_3)_3.C.OH$, not containing hydrogen linked on to the already oxidized carbon atom, further oxidation is not so easy, and energetic reagents are necessary, when the molecule breaks down into substances of smaller carbon content.

3.


Although the above may be taken as a short summary of the effects of oxidation on aliphatic substances (the aromatic will be discussed later), yet the nature of the actual oxidation processes which have been observed to take place on the passage of organic substances through the animal organism are of a different order from those carried out in the laboratory.

Such changes are characterized by a striking selective oxidizing action; thus an animal capable of completely breaking down many hundred grains of sugar to its end products in twenty-four hours is incapable of similarly treating say a few grains of sodium formate, which to the extent of 50–70 per cent. of the dose taken is eliminated unchanged in the urine. Further than this, of these two changes the latter is much more readily carried out in the laboratory than the former. Then dextrose and laevulose are completely decomposed by the body cells, but the sexvalent alcohol mannite passes through with very little change. In this case the replacement of a $-CH_2OH$ group by CHO or



has been sufficient to bring about complete oxidation.

Even stereochemical isomerides are differently acted upon; thus, in alcaptonuria, naturally occurring phenylalanin,

$$C_6H_5.CH_2.CHNH_2.COOH,$$

is almost quantitatively oxidized to homogentisinic acid,

$$C_6H_3(OH)_2.CH_2.COOH,$$

whereas the racemised form is only oxidized to the extent of 50 per cent. Then *m*- and *l*-tartaric acids are much more completely

broken down by the organism than are *dextro*-tartaric and racemic acids, and this latter acid is not decomposed into its optical isomerides. In this connexion it may be mentioned that Chabrié found that *l*-tartaric is more toxic than the *dextro* form, and both of these more than racemic acid; for instance, the following amounts produce the same action: 34·26 gms. *l*, 104·24 gms. *d*, and 165·25 gms. racemic acid.

The few examples given clearly show the characteristic selective action of the tissues, oxidizing some substances completely, rejecting others with but slight chemical or physical differences.

Our ignorance of the manner in which the actual process of oxidation takes place is readily realized when it is remembered that no single case is known of the complete oxidation of an organic substance in aqueous solution by the oxygen of the air. Nencki attempted to determine, without success, the extent of the oxidation of sugar and albumen on exposure in alkaline solutions to the air at a temperature of 36° C.; the amount was extremely small.

The problem is further complicated by the observation that in some cases the oxidizing action may be depressed, in others increased, by the simultaneous dosage with other substances; thus Nencki and Sieber[1] found that while the body of a healthy man could form ·82 gm. of phenol from 2 gms. of benzene, under normal conditions this amount dropped to ·33 gm. if 2 gms. of alcohol per kilo. body weight were simultaneously administered. Pflüger, Poehl, and others have shown that under other conditions the oxidizing action of the animal organism may be increased.

It is not proposed to discuss the various hypotheses that have been brought forward in this connexion. Traube assumed the existence of oxidizing enzymes, afterwards shown to be present in the lungs, kidney, muscles, &c., by Schmiedeberg, Salkowski, Jaquet, &c., but their action appears to be very limited, quite insufficient to account for the variety of known oxidation processes, although in all probability they play some part in these changes.

The suggestion that in some way or other the oxygen is activated in the body is difficult to follow; it is more probable that, as Pflüger has suggested, it is not the oxygen that is activated, but that the activity is a function of proteins of the living protoplasm.

[1] *Pflüg. Arch.*, 31, 319.

(a). OXIDATION OF ALIPHATIC SUBSTANCES.

Hydrocarbons. The oxidation of the hydrocarbons of the aliphatic series on their passage through the organism has not yet been observed, and as may be gathered from the previous remarks is hardly to be expected. It follows that if the petroleum emulsions have any therapeutic value, it cannot depend on any analogy to cod liver oil, which is readily utilized by the organism, i.e. broken down to its end oxidation products. In fact these bodies taken by the mouth are completely eliminated in an unchanged condition in the faeces.

Primary alcohols are oxidized, either completely or, in some cases, to the corresponding acid, but, as might be expected, the unstable intermediate aldehydes are never found in the body; if produced at all they are but transitory products to the higher stage of oxidation. Formaldehyde, a saturated solution of which is termed **formalin**, probably owes its remarkable antiseptic properties to the ease with which it abstracts oxygen and becomes formic acid, a process which causes the breakdown of organic matter.

Combinations of formaldehyde with indifferent organic bodies, such as milk and sugar are free from toxic effects,[1] and on being introduced into the animal system it is found that one-quarter passes directly into the urine, one-tenth combines with ammonia, giving hexamethylene tetramine, but the largest part is found as formic acid.

On the other hand, chloral, $CCl_3.CHO$, and butyl chloral, $CCl_3.CH_2.CHO$, are not oxidized to their corresponding acids, but reduced to alcohols and eliminated, as previously mentioned, as compounds of glycuronic acid.

The animal organism appears to exercise a greater power of oxidizing ethyl, propyl, or butyl groups than it possesses over methyl; thus methyl alcohol, or its esters, and methylamine or methyl nitrile, give formic acid, whereas ethyl alcohol or ethylamine are completely broken down, and the higher nitriles, which are much more toxic than methyl nitrile, are converted into sulphocyanides. As regards the secondary alcohols, Albertoni has shown that isopropyl alcohol, $CH_3.CHOH.CH_3$, is partly oxidized to acetone, $CH_3.CO.CH_3$, and partly unchanged.

The tertiary alcohols, such as amyl alcohol or trimethyl carbinol,

[1] J. Jacobsen, *Chem. Cent. Blatt.*, 8, 693, 1906.

more difficult to oxidize than either primary or secondary, pass through the body unchanged. The replacement of hydrogen by chlorine causes an increase in the stability of the alcohols towards oxidizing agents; thus trichlorethyl alcohol, $CCl_3 . CH_2OH$, and trichlorbutyl alcohol, $CCl_3 \cdot CH_2 . CH_2OH$, pass unchanged through the animal organism, and are eliminated as glycuronic derivatives. A corresponding protection is noticed in the case of the organic acids, whereas acetic acid, $CH_3 . COOH$, is readily oxidized; trichloracetic acid or trichlorbutyric acid are only partially decomposed.

A similar protection against the oxidizing action of the organism is noticed in the case of the sulphonic acid group; both ethyl sulphate,[1]

$$SO_2 \begin{matrix} OC_2H_5 \\ OH \end{matrix}$$

and sulphoacetic acid,

$$CH_2 \begin{matrix} SO_2OH \\ COOH \end{matrix}$$

passing through the body unchanged.

As regards the polyhydric alcohols, glycerol,

$$\begin{matrix} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{matrix}$$

is readily oxidized, but mannite,

$$\begin{matrix} CH_2OH \\ | \\ (CHOH)_4 \\ | \\ CH_2OH \end{matrix}$$

only partially, whereas the sugars,

$$\begin{matrix} CH_2OH \\ | \\ (CHOH)_4 \\ | \\ CHO \end{matrix} \quad \text{and} \quad \begin{matrix} CH_2OH \\ | \\ (CHOH)_3 \\ | \\ CO \\ | \\ CH_2OH \end{matrix}$$

Dextrose. Laevulose.

are of course completely broken down.

[1] kowski, *Pflüg. Arch.*, 5, 357.

Passing to the final oxidation products of the primary alcohols, i. e. the group of acids, their complete breakdown into carbon-dioxide and water is as a rule effected with greater difficulty than that of the alcohols or aldehydes, yet in the animal organism this process takes place with great ease. With the exception of formic acid, the fatty acids are easily oxidized, and as their molecular magnitude increases and stearic, $CH_3(CH_2)_{16}.COOH$, palmitic, $CH_3(CH_2)_{14}.COOH$, and the unsaturated oleic,

$$C_8H_7.CH:CH(CH_2)_7.COOH,$$

acids are reached, these in the form of their glycerol esters constitute the important group of food-stuffs, the fats.

Oxy-acids, such as glycolic acid, $CH_2OH.COOH$, β-oxybutyric, $CH_3CHOH.CH_2.COOH$,[1] lactic acid,

$$CH_3.CH\begin{matrix}OH\\COOH,\end{matrix}$$

are easily oxidized, but in phosphorus poisoning and in several pathological conditions this latter acid appears in the urine. In this connexion β-oxybutyric acid, $CH_3.CHOH.CH_2.COOH$ (and its oxidation product acetoacetic acid, $CH_3.CO.CH_2.COOH$), may be mentioned; as is well known these occur in diabetes.

Conflicting statements are met with as regards oxalic acid; some state that it passes unchanged into the urine, whilst Marfori found that a considerable amount was fully oxidized, and that the same process takes place with sodium oxalate, of which 30 per cent. of the amount taken reappears in the urine. Faust found that the whole of this acid injected into a dog could be recovered from the urine. Malonic acid, $CH_2(COOH)_2$, is largely destroyed, only traces passing through unchanged; tartronic acid, $CHOH(COOH)_2$, is completely broken down, and so are succinic,

$$\begin{matrix}CH_2.COOH\\|\\CH_2.COOH\end{matrix}$$

and, to a very large extent, tartaric acid (see p. 70),

$$\begin{matrix}CH.OH.COOH\\|\\CH.OH.COOH\end{matrix}$$

[1] G. Satta, *Beitr. Chem. Physiol. Path.*, 6, 1–26, 1904.

and malic acid,

$$\begin{array}{l} CH.OH.COOH \\ | \\ CH_2.COOH \end{array}$$

Only very small amounts of glutaric acid,

$$CH_2\begin{array}{l} \diagup CH_2.COOH \\ \diagdown CH_2.COOH \end{array}$$

escape oxidation.

Amido acids given in moderate amounts are completely broken down, the nitrogen appearing as urea. Glycocoll, $CH_2.NH_2.COOH$, and leucin, $CH_3.(CH_2)_2.CHNH_2.COOH$, even in large amounts, never appear in the urine, whereas alanin, $CH_3.CHNH_2.COOH$, aspartic acid,

$$\begin{array}{l} CH.NH_2.COOH \\ | \\ CH_2.COOH \end{array}$$

and glutaminic acid,

$$CH_2\begin{array}{l} \diagup CHNH_2.COOH \\ \diagdown CH_2.COOH \end{array}$$

are partially oxidized, and partially pass through the organism unchanged.[1]

Wohlgemuth[2] has found that rabbits fed with racemised tyrosin, leucin, aspartic acid, and glutaminic acid oxidized the optical isomeride occurring normally in the body, whilst the other was partially or completely excreted in the urine. Thus *d*-tyrosin is the form in which this substance occurs normally in animals, and when the racemised form is given, *d*- is destroyed and *l*- found in the urine.

The acid amides, with exception of acetamide, $CH_3.CONH_2$, and oxamide,

$$\begin{array}{l} CONH_2 \\ | \\ CONH_2 \end{array}$$

which are but partially oxidized, are as completely broken down as their corresponding acids. The nitriles of the acetic acid series, formed by the dehydration of the corresponding ammonium salt, e. g.

$$CH_3.COONH_4 - 2H_2O = CH_3CN,$$

[1] Stolte, *Hofmeister's Beiträge*, 5, 15, 1903.
[2] *Ber.*, 38, 2064, 1905.

which are fairly readily converted back into the acids by the action of dilute acids or alkalis, e. g.

$$CH_3CN + 2H_2O = CH_3COONH_4$$

are not, with the exception of the lowest member CH_3CN, decomposed in this manner on their passage through the organism, but, as previously mentioned, are converted into sulphocyanides (see p. 65). Methyl nitrile, which is the least toxic member of the group, is oxidized to formic acid, but with the higher homologues no organic acid is formed.

(b). OXIDATION OF AROMATIC SUBSTANCES.

As regards the members of this series, the breakdown of the benzene nucleus itself is only of the rarest occurrence, the changes which are effected on the passage of aromatic substances through the organism being confined to alterations in the substituting groups or replacement of hydrogen atoms in the benzene ring.

Phenylalanin, $C_6H_5 . CH_2 . CH.NH_2 . COOH$, tyrosin,

$$C_6H_4\begin{matrix}OH\\ OH_2\end{matrix} . CH.NH_2 . COOH$$

and α-amido cinnamic acid,

$$C_6H_5 . CH : CH\begin{matrix}NH_2\\ COOH\end{matrix}$$

occupy a unique position among the aromatic derivatives, since they are almost completely oxidized in the body, whereas phenyl propionic, $C_6H_5CH_2 . CH_2 . COOH$, and cinnamic acids,

$$C_6H_5CH : CH.COOH,$$

are changed into benzoic. So far as is known, only two cyclic compounds of the benzene series occur in combination in the protein molecule, viz. tyrosin and phenylalanin, and it is interesting to observe that these are among the very few substances known which are completely oxidized by the animal organism.

In this connexion it is interesting to note that in alcaptonuria, phenylalanin, tyrosin, and α-phenyl propionic acid give rise to homogentisinic acid,[1] and that the naturally occurring optically active phenylalanin is converted almost quantitatively, whereas the racemised form is only changed to the extent of 50 per cent.

[1] Neubauer, Falta, *Zeit. f. physiol. Chem.*, **42**, 81, 1904.

According to Juvalta[1], phthalic acid and also phthalimide,[2]

$$C_6H_4\langle\begin{matrix}COOH\\COOH\end{matrix}\ 1:2 \text{ and } C_6H_4\langle\begin{matrix}CO\\CO\end{matrix}\rangle NH,$$

are broken down, in the case of the former substance to the extent of over 57 per cent. of the amount given. Pribram[3] states that phthalic acid is excreted quantitatively in the rabbit.

Methyl quinoline is stated by Rudolf Cohn to be almost completely oxidized in the body, and the same author showed that 1:2-nitrobenzaldehyde to a large extent underwent the same fate, and that only small amounts were oxidized to the corresponding 1:2-nitrobenzoic acid.

Benzene itself is oxidized to phenol, and also 1:4- and 1:2-dioxybenzene, but the oxidation does not go further, since 1:2-dioxybenzene is eliminated unchanged. Naphthalene is eliminated as a glycuronic derivative in a similar manner to the β-oxy derivatives (β-naphthol).

The homologous benzenes undergo similar changes to those previously mentioned (p. 30), the side-chains being oxidized and replaced by COOH. Thus toluene, $C_6H_5CH_3$, gives benzoic acid,

$$\text{xylene, } C_6H_4\langle\begin{matrix}CH_3\\CH_3\end{matrix}, \text{ gives toluic acid, } C_6H_4\langle\begin{matrix}CH_3\\COOH\end{matrix}$$

and mesitylene, $C_6H_3(CH_3)_3$ 1:3:5, gives mesitylenic acid, $C_6H_3(CH_3)_2COOH$. Ethyl benzene, $C_6H_5.CH_2.CH_3$, is also oxidized to benzoic acid. Propyl benzene, $C_6H_5.CH_2.CH_2.CH_3$, behaves similarly, giving rise to the same acid, although isopropyl benzene, $C_6H_5.CH(CH_3)_2$, is oxidized in the ring to a phenol-like derivative. This may be compared with the behaviour of cymene,

$$C_6H_4\langle\begin{matrix}CH(CH_3)_2\\CH_3\end{matrix}\ 1:4,$$

which Ziegler showed gave cumic acid,

$$C_6H_4\langle\begin{matrix}CH(CH_3)_2\\COOH\end{matrix}\ 1:4.$$

Now when the hydrocarbon is treated with powerful oxidizing agents, such as dilute nitric acid or chromic acid, the propyl group is first attacked, giving

[1] Juvalta, *Zeit. f. physiol. Chem.*, **13**, 26.
[2] Koehne, *Chem. Centr.*, **2**, 296, 1894.
[3] *Chem. Centr.*, **2**, 668, 1904.

$$C_6H_4\begin{cases}COOH\\CH_3\end{cases}\ 1:4;$$

but when a mild agent, such as caustic soda and oxygen (air), is employed, the methyl group is oxidized.

1 : 2-Nitrotoluene,

$$C_6H_4\begin{cases}NO_2\\CH_3\end{cases}$$

is oxidized to the alcohol

$$C_6H_4\begin{cases}NO_2\\CH_2OH\end{cases}$$

and eliminated as a glycuronic acid derivative.

Generally speaking, such radicals as CH_3, $CH_2.OH$, CHO, and $CH_2.NH_2$, attached to the benzene nucleus, are oxidized to —COOH [1] and eliminated as hippuric acid (p. 63).

Phenyl propionic acid,

$$C_6H_5.CH_2.CH_2.COOH,$$

and cinnamic acid, $CH_5CH:CH.COOH$, are converted into benzoic acid, but phenyl acetic acid, $C_6H_5.CH_2.COOH$, gives phenaceturic acid, $C_6H_5CH_2.CONH.CO.NH_2$, and mandelic acid,[2]

$$C_6H_5.CH\begin{cases}OH\\COOH,\end{cases}$$

passes through the organism unchanged, whereas phenylamido acetic acid,

$$C_6H_5.CH\begin{cases}NH_2\\COOH\end{cases}\ \text{gives}\ C_6H_5.CH\begin{cases}OH\\COOH.\end{cases}$$

Now since phenyl propionic acid gives benzoic acid, it cannot pass through the stage of phenyl acetic acid, and consequently Knoop considers that the oxidation of that acid can only take place in the β position. As previously mentioned, ethyl benzene, $C_6H_5.CH_2.CH_3$, (p. 76) gives benzoic acid, and it is probable that the CH_2 group is attacked first, and not the methyl; this is borne out by the fact that acetophenone, $C_6H_5COCH_3$, also gives benzoic acid. Other acids investigated by Knoop containing more than two carbon atoms in the side-chain did not give benzoic acid. An analogous oxidation of hydrogen in the β position is seen in the formation of β-oxybutyric acid, $CH_3.CH.OH.CH_2.COOH$, and the further oxidation products, acetoacetic acid, $CH_3.CO.CH_2.COOH$, and acetone, $CH_3.CO.CH_3$, in diabetes.

[1] Knoop, *Hofmeister's Beiträge*, **6**, 150, 1904.
[2] Schotten, *Zeit. f. physiol. Chem.*, **8**, 68, 1884.

In many cases oxidation in the nucleus takes place provided that the hydrogen in the 1 : 4 position to the group already present is not itself substituted. Thus aniline, $C_6H_5NH_2$, is partially oxidized to 1 : 4-amidophenol,

$$C_6H_4\begin{matrix}OH\\NH_2\end{matrix}$$

K. Klingenberg showed that diphenyl,

$$\begin{matrix}C_6H_5\\|\\C_6H_5\end{matrix}$$

gives the sulphuric ester of 1 : 4-oxydiphenyl,

$$\begin{matrix}C_6H_4.OH\ 1:4\\|\\C_6H_5\end{matrix}$$

Phenyl methane gives 1 : 4-oxyphenyl methane, and a similar type of action is noticed with chlor-, brom-, and iodo-benzene, which gives rise to cystein derivatives, in which the H atom in the 1 : 4 position to the halogen atom has been attacked (see p. 66). On the other hand,

Benzidine, $\begin{matrix}C_6H_4NH_2\ 1:4\\|\\C_6H_4NH_2\ 1:4\end{matrix}$ 1 : 4 Dibromdiphenyl, $\begin{matrix}C_6H_4Br\ 1:4\\|\\C_6H_4Br\ 1:4\end{matrix}$

are not oxidized by the animal organism. Nölting, who examined a large number of cases, states that the hydrogen of the benzene nucleus is only replaced by hydroxyl (OH) in the para position to the substituting group, and should this position be occupied such a type of oxidation does not take place.

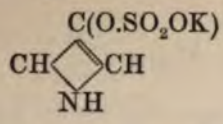
From a physiological point of view the oxidation of indol,

$$C_6H_4\begin{matrix}CH\\NH\end{matrix}\!\!>\!CH,$$

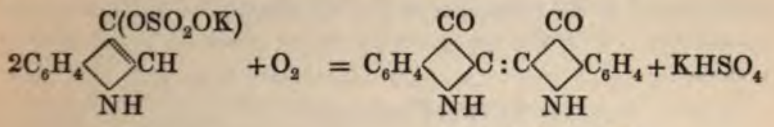
in the organism is of considerable importance. When this substance (which has distinct but not very marked toxic properties) is formed in the intestine as the result of putrefaction, or is introduced experimentally, absorption rapidly takes place; and it undergoes oxidation, most probably in the cells of the liver, to indoxyl,

$$C_6H_4\begin{matrix}C(OH)\\\diagdown\!\!\diagup\\NH\end{matrix}\!\!>\!CH,$$

which is eliminated as the potassium sulphuric ester



This ester is known as urine indican, owing to the fact that it was supposed to be identical with the indican of plants, which is not the case; this derivative on further oxidation gives indigo blue, which produces a characteristic colour in the urine.



Indigo blue.

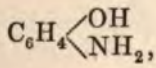
C. REDUCTION.

The direct reduction of the oxidized derivatives of the aliphatic and aromatic series, such as alcohols, acids, phenols, ketones, back to the hydrocarbons from which they are derived is by no means an easy matter, and powerful reagents are required, and it is not to be expected that such changes should occur during the passage of these derivatives through the animal organism.

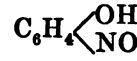
The cases of substances undergoing a process of reduction on their passage through the organism are, relatively to oxidation, very rare. One of the most interesting is that of chloral, CCl_3CHO, and butyl-chloral, $CCl_3 . CH_2 . CHO$, which are reduced to their corresponding alcohols and eliminated as compounds of glycuronic acid (see p. 60), this process being much more difficult to accomplish in the laboratory than the opposite one of oxidation to the corresponding acids trichlor-acetic and β-trichlorpropionic.

In the aromatic series the easily reduced quinone undergoes this change in the organism, and is eliminated as hydroquinone.

Other examples of reduction are met with in the case of some nitro compounds. Thus Eric Meyer has shown that nitrobenzene is partially converted into 1 : 4-amidophenol,

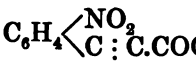


but chiefly eliminated unchanged. Similarly 1 : 3- and 1 : 4-nitrophenol,



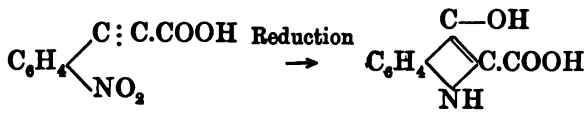
give some of their corresponding amido derivatives. The case of nitrobenzaldehyde has been previously alluded to (p. 65).

G. Hoppe-Seyler has shown that 1 : 2-nitrophenylpropiolic acid,

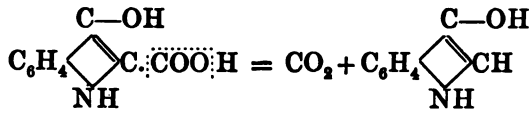


is eliminated as the potassium salt of the conjugated sulphuric ester of indoxyl. This change probably takes place in the following manner :—

1.

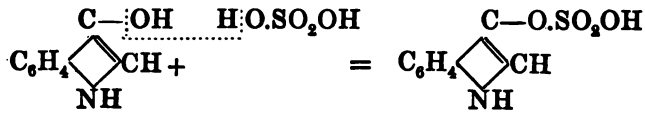


2.



Indoxyl.

3.



Indoxyl-sulphate.

Many organic dyes, such as alizarin blue or indophenol blue lose their colour while in the cells and fluids of the body, but regain it on exposure to air.

CHAPTER IV

THE ALCOHOLS AND THEIR DERIVATIVES. THE MAIN GROUP OF ANAESTHETICS AND HYPNOTICS. I. General physiological action of anaesthetics and hypnotics. Overton-Meyer theory. Traube. Moore and Roaf on Chloroform. Baglioni's theory.

II. Method of preparation and chemical and physiological properties of the Alcohols. Esters of Halogen acids, Nitrous and Nitric, Sulphurous and Sulphuric acids. The Ethers.

I. GENERAL OUTLINES OF THE PHYSIOLOGY OF HYPNOTIC AND ANAESTHETIC DRUGS.

THE distinction between the pharmacological groups of anaesthetics and narcotics is important in practice, but does not depend upon differences in physiological action or chemical constitution. For the production of general anaesthesia, volatile bodies, which are rapidly absorbed and excreted, are most suitable, whereas less volatile liquid or solid substances, whose activity is only gradually set free in the organism, can more conveniently be employed for producing hypnosis. The latter condition can of course be produced by small doses of a body like chloroform, but the method of administration is inconvenient, and the resulting sleep rapidly passes away. On the other hand, large doses of a narcotic like chloral hydrate may produce complete surgical anaesthesia; indeed this body was used intravenously for a short time in the middle of last century, and major operations performed under its influence. The disadvantage of such a procedure is that the dosage has to be too high for the complete safety of the patient.

The physiological action of the entire group of aliphatic narcotics is first on the higher centres of the cerebrum, then on the lower centres of the medulla and cord. Eventually the reflexes are

completely abolished, and this constitutes an important distinction between this group and the alkaloidal narcotics of which the chief representative is morphine. In large doses this substance increases reflex irritability, and in small doses does not depress it.

The aliphatic narcotics belong to several chemical groups, the chief being the alcohols, aldehydes, ketones, and their derivatives.

Though it appears doubtful whether methane itself is narcotic, ethane and acetylene are direct narcotics. Those which belong to the alcohol group owe their specific action to the hydrocarbon radicals, not to the hydroxyl. When the latter are increased the narcotic action is diminished; but the hydroxyl radicals may be anchoring groups. As a rule ethyl compounds are more powerfully hypnotic than methyl, especially when occurring in bodies which offer some resistance to oxidative processes.

The entrance of carboxyl appears to stop all narcotic effects, though the esters containing an alkyl group in place of the hydrogen of the carboxyl radical are active. Thus urethane,

owes its activity to the ethyl group. The higher the molecular weight of the alcoholic group the more powerful is the hypnotic action.

Thus **hedonal,**

is much more powerful than urethane. The aldehydes and ketones are not as a rule convenient narcotics, as they cause a marked preliminary stage of excitement.

Many of the aldehyde derivatives, unsubstituted by halogens, are only feebly narcotic, the parent substances being often irritant. The ketones themselves have not yielded any bodies of great practical importance, although among their derivatives are the valuable sulphones.

The introduction of a halogen, especially chlorine, greatly enhances the narcotic power, but these compounds have the great disadvantage of being respiratory and cardiac depressants. The other halogen elements have a still more deleterious effect.

There remain for consideration several points of a theoretical

character as to the general processes which underlie the production of narcosis.

1. The researches of Overton showed the velocity with which substances diffuse into the protoplasm; these are divided into four groups, the first diffuse rapidly, the second less, the third least, and the fourth group contains those bodies for which the cells are completely impermeable.

Class I. Univalent alcohols, aldehydes, ketones, aldoximes, and ketoximes, nitro-alkyl and cyanides, neutral esters of the inorganic and many organic acids, aniline, pyridine, and the majority of the free alkaloids.

Class II. The divalent alcohols and amides of mono-carboxylic acids.

Class III. Glycerol, urea, the hexoses and amido-acids are only very slightly diffusable.

Class IV. Salts of strong inorganic acids, inorganic acids and bases.

The permeability increases in homologous series, and by the replacement of hydrogen by methyl or methyl by ethyl, &c.

Now, as a very general rule, the rapidity of diffusion into membranes depends upon the solubility of substances in such bodies as fats, cholesterin, and lecithin, and Overton has brought forward the hypothesis that the magnitude of the distribution coefficient between fat and water determines the velocity of osmosis. Both Overton and Hans Meyer draw attention to the fact that as a rule narcotics, anaesthetics, and antipyretics are substances which diffuse rapidly, and they consequently conclude that the *narcotic value of a drug depends principally on its solubility in lipoid substances.* Although narcotics are all more or less soluble in water, there is no direct relationship between this solubility and narcotic power. Meyer tabulated the aliphatic narcotics according to the smallest molecular concentration which produced definite physiological effect, the values being expressed as fractions of the normal solution (1 gm. molecule per litre), and termed 'liminal values'.

If these are compared with the 'distribution coefficient', i.e. the ratio of the solubility in fats S_F to their solubility in water S_W, it is found that the liminal values are smallest when the distribution coefficient is high—the most powerful narcotics are those which are most soluble in oil or fat and least soluble in water.

	Liminal Value.	Distribution. Coefficient $\frac{S_F}{S_W}$
Trional	·0018	4·46
Tetronal	·0013	4·04
Sulphonal	·006	1·11
Butylchloral hydrate	·002	1·59
Bromal hydrate	·002	·66
Chloral hydrate	·02	·22
Ethyl methane	·04	·14
Methyl methane	·4	·04
Monacetin	·05	·06
Diacetin	·015	·23
Triacetin	·01	·3
Chloralamide	·04	
Chlorhydrin	·04	
Dichlorhydrin	·002	

In the sulphone derivatives it was found that those most soluble in fat were also those that showed greatest physiological activity, whereas in this series Baumann and Kast had traced this activity to the presence of ethyl groups.

	Action.	Distribution Coefficient.
Dimethyl-sulpho methane	very slight	·106
Dimethyl-sulpho ethane	slight	·151
Sulphonal	marked	1·115
Trional	more marked	4·46
Tetronal	more marked	4·04

Mansfield has recently shown that some narcotics have more powerful action when given to starved animals than is the case when the animals are well fed. This, he suggests, may be due to the fact that in the latter the *tissue* fats absorb some of the narcotic and render it incapable of acting on the central nervous system.

The Overton-Meyer theory then, based on the above observations, is that indifferent substances gain access to the cells of the central nervous system owing to their solubility in the cell lipoids in which these cells are particularly rich, and that gradations in narcotic power are due to the presence of groups which increase the partition coefficient, i. e. which render the derivatives more soluble in such fatty substances. The theory only explains the presence of the active substance in the cell, and when this has been effected we are in complete ignorance of the next phase, although it is fairly obvious that there will be great differences between inert substances, of the nature of ether or chloroform, and bodies which are chemically active, such as aniline. The Overton hypothesis further would lead to the supposition that cells rich in lipoid substance should show a preferential absorption; that this is not always the case is seen in the

fact that the aliphatic narcotics do not attack the peripheral nervous system, which contains a large amount of such bodies. Further, Cushny has pointed out that many benzene derivatives have a high distribution coefficient, though without narcotic action.

J. Traube differs from Overton in his views as to the manner in which the substance enters the cell, and considers that it is not the content of lipoid which determines the sequence or the amount of osmosis. He ascribes the direction and velocity of osmosis to the difference of the surface tensions, as he does not hold the prevailing views as to the nature of osmotic pressure. Rapid penetration into the cells seems to be the most essential condition for enabling a narcotic substance to exercise its paralysing and other effects on the interior of certain cells, and 'we have found that a near relation exists between osmotic velocity and surface tension, and therefore we can expect that surface tension and narcotic power run parallel'. This he finds is really the case, even when most varied types of narcotics are compared. Traube considers that when the drug has thus gained entrance to the cell it may exercise its narcotic power in proportion to its solubility in the cell lipoids.

Moore and Roaf have recently promulgated the theory that anaesthetic substances form unstable compounds with the cell proteins, which only last so long as sufficient partial pressure of the gas in the tissue fluids is maintained. Beginning with solutions of blood serum and haemoglobin, and continuing their investigations with extracts of living tissues (brain, heart, lungs, &c.), they showed that at higher pressures chloroform and other anaesthetics did not obey the ordinary laws of solution, although their curves, examined in the light of the phase rule, exclude the hypothesis of the formation of chemical compounds. Other anaesthetic substances varied in the degree to which this took place, but no variation in kind was found among them.

It appears quite possible that adsorption constitutes the mechanism by which substances of narcotic nature are taken up in the cells. Moore and Roaf's vapour pressure curves for chloroform and serum have the characteristic form of adsorption curves. Gibbs has shown that the further the surface tension of a liquid is depressed by the dissolved substance, the greater will be its adsorption; it is moreover a general principle that chemical action is proportional to concentration; the latter will be greatest when solubility and, hence, distribution ratio are greatest. It seems to the present writers that these general principles include the essential

basis of the previous hypotheses. The substance enters the cell by adsorption, and the magnitude of its effect depends on its concentration.

What next takes place is pure conjecture, but in the case of some substances a parallel may be drawn with the so-called catalytic reactions. Bredig has shown that the rate of decomposition of solutions of hydrogen peroxide by colloidal platinum is roughly proportional to the concentration of the latter substance; the action is hindered, that is 'poisoned', by the presence of traces of carbon-monoxide (almost without exception blood poisons act similarly), but on its removal the decomposition proceeds as before. Now the conversion of the total platinum into a compound by the 'toxic' substance is out of the question, owing to the extreme disparity of the amounts of the two substances. Thus, approximately, in a $\frac{1}{10}$ normal solution of hydrogen peroxide containing $\frac{1}{10000}$ colloidal platinum an amount of carbon monoxide $= \frac{N}{10,000,000}$ is sufficient to stop the action. If this is compared to the action of chloroform, for instance, it will be seen that after adsorption has taken place its further action may be compared to that of carbon monoxide in the example given above.

Strychnine also plays a corresponding rôle, bringing about reactions out of all proportion to the quantity employed.

It is generally supposed that the reaction brought about by colloidal platinum takes place in the adsorbed layer on the surface of the platinum particles; the poisons will also be absorbed, and either by further chemical action or purely physical means coat and, hence, isolate the active surface with an inert layer. The corresponding picture will be life processes taking place through the agency of similar colloidal substances. The actions may be depressed, as the oxidation processes appear to be by the administration of ether or chloroform, or the velocity with which they are taking place may be enormously increased, as perhaps may be the case with strychnine.

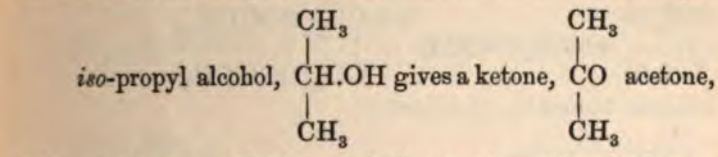
Baglioni has formulated a theory of narcosis based on observations on the various groups of benzene phenol derivatives. One of these groups, containing acetanilide, phenylhydrazine, benzylalcohol, benzaldehyde, acetophenone, benzoic acid, and salicylic acid, produces paralysing effects only, without convulsions. The amount of paralysis produced varies inversely as to the amount of oxygen present in the side-chain. Thus benzylalcohol is a powerful paralysing agent; benzaldehyde is less powerful, and benzoic acid least. He

thus concludes that narcotic effect also depends on the power to withdraw oxygen from the 'inogen' compounds in the central nervous system; that is, that narcosis is a reducing process. Deprivation of oxygen, as by breathing CO_2, or inert gases, such as hydrogen, gives rise to a series of symptoms corresponding to chloroform narcosis. Herter has shown, by means of methylene blue injections, that chloroform, ether and chloralhydrate (as likewise low temperatures) markedly diminish the oxidizing capacity of the tissues.

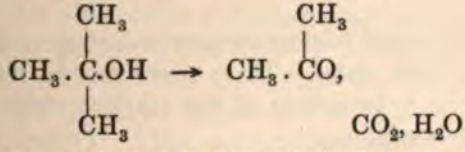
II. THE ALCOHOLS OF THE ALIPHATIC SERIES.

The group of alcohols may be regarded as derived from water by the replacement of one hydrogen atom by an hydrocarbon radical; they consequently contain the so-called hydroxyl group, and their properties depend, to a very large extent, upon the nature of the hydrocarbon complex to which this is joined.

The primary contain the group :CH_2OH, the secondary :CH.OH, and in the tertiary alcohols the hydroxyl group is linked on to a carbon carrying no hydrogen atoms, e. g. $(CH_3)_3C.OH$. As previously mentioned (p. 68), the nature of their oxidation products, among the most important of the aliphatic derivatives, is dependent upon the presence of these groupings. Thus a primary alcohol, such as ethyl alcohol, $CH_3.CH_2OH$, gives rise firstly to an aldehyde, acetaldehyde, $CH_3.CHO$, which passes, on further oxidation, to an acid, acetic acid, CH_3COOH. On the other hand a secondary, such as



whereas a tertiary alcohol on similar treatment breaks down, giving ketones or acids of smaller carbon content, e. g.



Those alcohols which contain the radical of the aromatic hydrocarbons attached to hydroxyl, such, for example, as phenol, $C_6H_5.OH$, show such striking differences both chemically and physiologically to the aliphatic derivatives that they will be described separately.

Methyl alcohol, $CH_3.OH$, the simplest member of the series, is one of the products of the dry distillation of wood. Ethyl alcohol, C_2H_5OH, is obtained by the fermentation of sugar, and, as previously mentioned (p. 36), is one of the chief starting-points for the preparation of the aliphatic derivatives. The various special methods which can be employed for the synthesis of members of this group will not be described; they are to be found in any textbook on organic chemistry, but the following three general methods of preparation are important.

General Methods of Preparation.

1. The monohalogen derivatives of the paraffins, and especially the iodides, are readily converted into alcohols, in many cases by simply heating with water to a temperature of 100°–120°; thus $C_2H_5I + H_2O = HI + C_2H_5.OH$. But since the reaction is reversible, e.g. $C_2H_5OH + HI = H_2O + C_2H_5I$, it may not take place to any great extent, a state of equilibrium being more or less rapidly attained. In consequence, as a very general rule, a base is required to combine with the liberated acid; thus with silver hydrate the reaction may take place at the ordinary temperature, whereas with lead oxide boiling is generally necessary.

In other cases the previous formation of the ester may be desirable; this is obtained by the interaction of the halogen derivative with either silver or sodium acetate, and on decomposition of the resulting substance with potash or soda the alcohol is readily obtained, e.g.

A. $\begin{matrix}CH_2Br\\|\\CH_2Br\end{matrix} + 2CH_3.COOAg = \begin{matrix}CH_2.(OOC.CH_3)\\|\\CH_2.(OOC.CH_3)\end{matrix} + 2AgBr$

Ethylene dibromide.

B. $\begin{matrix}CH_2.(OOC.CH_3)\\|\\CH_2.(OOC.CH_3)\end{matrix} + 2KOH = 2CH_3COOK + \begin{matrix}CH_2.OH\\|\\CH_2.OH\end{matrix}$

Glycol.

2. Another general method consists in decomposing the esters of sulphuric acid with water. These esters may be readily obtained by treating the hydrocarbons of the ethylene series with concentrated sulphuric acid, e.g.

A. $\begin{matrix}CH_2\\\|\\CH_2\end{matrix} + SO_2\begin{matrix}OH\\OH\end{matrix} = SO_2\begin{matrix}O.C_2H_5\\OH\end{matrix}$

Ethylene. Ethyl-sulphuric acid.

B. $SO_2\langle^{O.C_2H_5}_{OH} + H_2O = SO_2\langle^{OH}_{OH} + C_2H_5.OH.$

The esters which are formed by treatment of the unsaturated hydrocarbons with sulphuric acid contain the acid radical attached to the carbon which carries the least number of hydrogen atoms.

Thus $\begin{matrix}CH_2\\ \|\\ CH\\ |\\ CH_3\end{matrix}$ gives $\begin{matrix}CH_3\\ |\\ CH—O.SO_2OH\\ |\\ CH_3\end{matrix}$ and consequently the alcohol $\begin{matrix}CH_3\\ |\\ CH.OH\\ |\\ CH_3\end{matrix}$

and $\begin{matrix}CH_3\\ \diagdown\\ C : CH_2\\ \diagup\\ CH_3\end{matrix}$ gives $\begin{matrix}CH_3\\ \diagdown\\ C\langle^{CH_3}_{O.SO_2OH}\\ \diagup\\ CH_3\end{matrix}$ and consequently the alcohol $(CH_3)_3.C.OH.$

3. Derivatives of ammonia containing the amido group $.NH_2$ are all decomposed by nitrous acid in aqueous solution and the group replaced by hydroxyl, e. g.

$$C_2H_5NH_2 + HNO_2 = C_2H_5OH + N_2 + H_2O$$
Ethylamine.

$$CH_3.CO.NH_2 + HNO_2 = CH_3.CO.OH + N_2 + H_2O$$
Acetamide. Acetic acid.

$$CO\langle^{NH_2}_{NH_2} + 2HNO_2 = CO\langle^{OH}_{OH} (CO_2 + H_2O) + 2N_2 + 2H_2O$$
Urea. Carbonic acid.

General Properties.

The alcohols are neutral colourless compounds, and the lower members of paraffin series have a characteristic burning taste and smell, and their solubility in water decreases as the carbon content increases. Thus methyl, ethyl, and propyl alcohols are miscible with water in all proportions. Primary *n*-butyl alcohol is soluble in twelve parts of water. Those containing 4–11 carbon atoms are oils immiscible with water, and the higher members are solids.

Isomerism is first observed in the alcohols of the limit hydrocarbons in the case of those derived from propane, $CH_3.CH_2.CH_3$, which gives rise to a primary $CH_3.CH_2.CH_2OH$ and a secondary

$CH_3.CHOH.CH_3$ called *iso*-propyl alcohol, easily distinguished by their oxidation products.

The chemical characteristics of the group depend essentially on the presence of the hydroxyl group. Sodium and potassium replace the hydrogen of this radical, e.g. $C_2H_5.ONa$, giving rise to substances called alcoholates; these are readily decomposed by water, are employed in many synthetic processes, form valuable condensing agents, and may be used for the purpose of reducing nitro compounds of the aromatic series to the corresponding azoxy derivatives.

When acted upon by acids or acid chlorides the alcohols readily yield the esters, e.g.

$$C_2H_5OH + HCl = H_2O + C_2H_5Cl$$

$$C_2H_5OH + HNO_2 = H_2O + C_2H_5.ONO_2$$
Ethyl nitrite.

$$C_2H_5OH + H_2SO_4 = H_2O + C_2H_5O.SO_2OH$$
Ethyl sulphate.

$$C_2H_5OH + CH_3COOH = H_2O + CH_3COOC_2H_5$$
Ethyl acetate.

$$C_2H_5OH + PCl_5 = HCl + POCl_3 + C_2H_5Cl$$

$$C_2H_5OH + C_6H_5COCl = HCl + C_2H_5COOC_2H_5$$
Ethyl benzoate.

On dehydration, by sulphuric acid or zinc chloride, the alcohols are converted into unsaturated hydrocarbons, e.g.

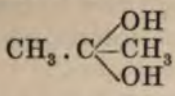
$$\begin{matrix} CH_2 & H \\ | & \vdots \\ CH_2 & OH \end{matrix} = H_2O + \begin{matrix} CH_2 \\ \| \\ CH_2 \end{matrix}$$

Polyhydric Alcohols.

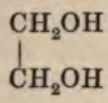
Besides containing one hydrogen atom replaced by hydroxyl, the hydrocarbons may have more, but it has been previously pointed out that, as a very general rule, one carbon atom cannot carry more than one hydroxyl group. Attempts to obtain $CH_2.CH(OH)_2$ by the action of silver hydrate, for instance, on $CH_3.CHCl_2$ always lead to the dehydration product of the unknown alcohol, i.e. the aldehyde,

$$CH_3.CH\begin{matrix} O & H \\ \vdots & \\ OH & \end{matrix} = H_2O + CH_3CHO$$

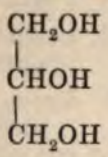
and in a similar manner $CH_3.CCl_2.CH_3$ does not yield



but the dehydration derivative $CH_3.CO.CH_3$ dimethylketone or acetone. Consequently the simplest dihydric alcohol is glycol,



which may be obtained by reactions similar to those previously described. With the entrance of a second hydroxyl group the solubility in water increases, but that in alcohol and ether decreases. At the same time the physiological activities decrease and almost entirely disappear in the case of the trihydric derivative glycerol,



a substance obtained by the saponification of fats in the soap industry.

These polyhydric alcohols show the same general chemical characteristics as the simpler ones previously described. As the number of hydroxyl groups increases so does the sweet taste; this property, not apparent in ethyl alcohol, CH_3CH_2OH, is noticed in glycol, $CH_2OH.CH_2OH$, and increases in glycerol and those pentahydric alcohols, such as mannitol, which are so closely related to the sugars, themselves pentahydroxy-aldehydes or ketones.

Physiological characteristics.

The entrance of the hydroxyl radical (OH) into aliphatic substances results in a decrease in their physiological reaction, a decrease which is still more marked as the number of such groups increases.

Thus the narcotic ethyl alcohol, $CH_3.CH_2OH$, passes to the inactive glycol, $CH_2OH.CH_2OH$, and propyl alcohol, $CH_3.CH_2.CH_2OH$, to the almost inert substance glycerol, $CH_2OH.CHOH.CH_2OH$. Glycerol is not absolutely without physiological action. In large doses it may produce restlessness and tremors, or even tetanic spasm. If given by the mouth or subcutaneously haemoglobinuria

may result, an effect unseen when glycerol is injected intravenously. Death may occur after toxic doses by respiratory failure.

Further, the aldehydes and ketones, with their marked physiological reactivity, become the inert sugars.

Caffeine loses its characteristic physiological reaction, and it is possible that in this case, as with the others, this decrease in reactivity may be ascribed to the drop in stability towards oxidizing processes, which follows the entrance of the hydroxyl grouping.

The alcohols act on the central nervous system, in particular on the cerebrum, the intensity of their actions depending upon the number of carbon atoms present, and increasing as the homologous series is ascended, although to some extent methyl alcohol is an exception.

Thus, in the case of rabbits :—

Methyl alcohol, CH_3OH, 6–12 gms. without action.
Ethyl „ C_2H_5OH, 7 gms. drunkenness, 12 gms. sleep.
n-Propyl „ C_3H_7OH, 12 gms. produce sleep in 5 minutes and death in 5 hours.
n-Butyl „ C_4H_9OH, 3 gms. produce drunkenness, 7 gms. sleep and death.
iso-Amyl- „ $(CH_3)_2CH.CH_2OH$, 2 gms. produce drowsiness.

The primary alcohols are less narcotic than the secondary, and these less than the tertiary. Thus :—

Iso-propyl alcohol, $CH_3.CHOH.CH_3$, 2 gms. produce drowsiness.
Methyl-ethyl carbinol, $CH_3.CHOH.C_2H_5$, 2 gms. produce drowsiness.
Diethyl „ $C_2H_5.CHOH.C_2H_5$, 2 gms. produce sleep.

In the case of the tertiary alcohols the action depends on the nature of the alkyl radicals attached to the carbon atom carrying the hydroxyl group. If that radical is methyl the reaction is relatively weak, but if ethyl the physiological reaction is largely increased (see p. 49), the increase varying with the number of such groups present, thus :—

Trimethyl carbinol, $(CH_3)_3C.OH$, 4 gms. produce sleep.
Dimethyl-ethyl carbinol, $\left.\begin{matrix}(C_2H_3)\\C_2H_5\end{matrix}\right\}C.OH$, 2 gms. produce 8 to 9 hours' sleep.
Triethyl carbinol, $(C_2H_5)_3C.OH$, 1 gm. produces 10 to 12 hours' sleep.

(Compare the substituted urea derivatives, p. 216.)

A similar characteristic is noticed in the pinacones, substituted derivatives of the physiologically inactive diprimary alcohol glycol

$$\begin{matrix} CH_2OH \\ | \\ CH_2OH \end{matrix}$$

thus :—

Methyl pinacone, $\begin{matrix} (CH_3)_2 . C.OH \\ | \\ (CH_3)_2 . C.OH \end{matrix}$ 10 gms. produce sleep.

Methyl-ethyl pinacone, $\begin{matrix} CH_3 \\ C_2H_5 \end{matrix}\!\!>\!C.OH$ $\begin{matrix} | \\ CH_3 \\ C_2H_5 \end{matrix}\!\!>\!C.OH$ 2 gms. produce sleep. Slight convulsions.

Ethyl pinacone, $\begin{matrix} (C_2H_5)_2.C.OH \\ | \\ (C_2H_5)_2.C.OH \end{matrix}$ Very insoluble. 1·5 gms. produce deeper and longer sleep. 3 gms. produce sleep after 2 hours.

Owing to the above observations Mering introduced **amylene hydrate,**

$$\left.\begin{matrix} CH_3 \\ CH_3 \\ C_2H_5 \end{matrix}\right\} C.OH,$$

in 1887 as a hypnotic. It is obtained from the unsaturated hydrocarbon amylene, by the general method previously described, i.e. through the agency of amylsulphuric ester. It has the hypnotic properties of an alcohol, but is also liable to produce symptoms of intoxication with nausea and headache. It is said to be a diuretic. It influences the heart and respiration like other amyl compounds.

DERIVATIVES OF THE ALCOHOLS.

A. THE ESTERS.

I. Aliphatic Esters of the Halogen Acids.

The esters are a group of substances in which the hydrogen atom of the acids is replaced by an organic radical; they consequently belong to two groups, (1) those obtained from the inorganic acids, and (2) those derived from the organic acids (see p. 122).

The former only will be discussed at this point, and the latter in connexion with the organic acids themselves. If the halogen acids, hydrochloric, hydrobromic and hydriodic be considered, it will be seen that on replacing the hydrogen by the radicals of the paraffins,

this group of substances results, thus HCl gives $CH_3.Cl$ or C_2H_5Cl, &c. From another point of view these derivatives may be looked upon as the halogen substitution products of the limit hydrocarbons, thus CH_4 acted upon by chlorine gives CH_3Cl,

$$CH_4 + Cl_2 = HCl + CH_3Cl.$$

But as the alcohols are invariably used in their preparation the former view may be adopted, and the two reactions compared

$$NaOH + HCl = NaCl + H_2O \mid CH_3OH + HCl = CH_3Cl + H_2O.$$

General methods of preparation.

1. The interaction of the alcohols and hydrochloric or hydrobromic acid is reversible and is not complete unless one of the substances formed is removed from the sphere of reaction. Thus in the case of methyl or ethyl alcohol, zinc chloride or sulphuric acid may be employed to remove the water formed. But with the higher alcohols unsaturated hydrocarbons may be firstly formed, and these add on the halogen acid in such a manner that isomers of the desired esters are obtained. Further, hydriodic acid, especially when in excess, is capable of reducing the iodides.

2. The phosphorus halogen derivatives readily react with the alcohols, giving rise to substances of this class,

$$PBr_3 + 3C_2H_5OH = 3C_2H_5Br + H_3PO_3$$

Phosphorus tribromide.

$$PI_3 + 3C_2H_5OH = 3C_2H_5I + H_3PO_3$$

Phosphorus tri-iodide.

phosphorus pentachloride easily gives the corresponding chloride.

General Properties.

The esters of the halogen acids are etherial, pleasant-smelling liquids, almost insoluble in water. The lower members are gases at ordinary temperatures, e.g. methyl chloride, ethyl chloride, and methyl bromide. The chlorides boil 20°–28° lower than the bromides, and these 28°–34° lower than the corresponding iodides. Their stability decreases from the chlorides to the iodides, and consequently their reactivity increases in the same direction. They are well adapted, especially the iodides, to the most varied series of synthetic reactions, many of which have been previously described (p. 87).

General Physiological characteristics following entrance of Chlorine.

The entrance of chlorine into aliphatic compounds increases their depressant effect on the heart, and as a very general rule increases their narcotic action. Their toxic action appears to stand in direct relationship to their narcotic properties, and the latter to increase with the amount of chlorine present. Thus methyl chloride, CH_3Cl, is less toxic than methylene chloride, CH_2Cl_2, and this less than chloroform, $CHCl_3$; the fully chlorinated methane derivative carbon tetrachloride, CCl_4; acts much more slowly and persistently than chloroform, and is usually stated to be a more powerful heart depressant, although Cushny describes it as only half as powerful as chloroform. Considerable interest consequently lies in the investigation of the results following the entrance of chlorine into a substance which acts as a heart stimulant. Thus caffeine has a stimulant action on the central nervous system and is a diuretic. In moderate doses it also stimulates the heart, an effect which can be produced by the local application of solutions of caffeine to the frog's heart. Chlorcaffeine is a much feebler cardiac stimulant; the other actions of caffeine, however, are still present (Pickering).

Then glycerin is physiologically inert, but the chlorhydrins have narcotic action and produce paralysis and dilation of the vessels. Monochlorhydrin, $CH_2OH.CHOH.CH_2Cl$, is the least and trichlorhydrin, $CH_2Cl.CHCl.CH_2Cl$, the most toxic.

The increase in narcotic properties following the entrance of chlorine, led to the introduction of trichlorisopropyl alcohol **Isopral**, $CCl_3.CHOH.CH_3$, by Impens in 1903. This substance may be formed by the action of methyl magnesium iodide (Grignard's reagent, see p. 38) on chloral and the decomposition of the resulting substance by water,

$$A.\quad CH_3.Mg.I + CCl_3CHO = CCl_3.C\begin{cases}H\\OMgI\\CH_3\end{cases}$$

$$B.\quad CCl_3.C\begin{cases}H\\OMgI\\CH_3\end{cases} + H_2O = MgI.OH + CCl_3.C\begin{cases}H\\OH\\CH_3\end{cases}$$

but its action on the heart is more powerful than chloral, and consequently it cannot be given in heart disease.

Similarly trichlorbutyl alcohol,

$$\begin{matrix}(CH_3)_2\\CCl_3\end{matrix}\!\!>\!C.OH + \tfrac{1}{2}H_2O$$

Chloretone has been introduced as an antiseptic, anaesthetic, and hypnotic. It is also known as **aneson** or **anesin** (a one per cent. solution of acetone chloroform). It is not a very toxic substance, the dose being ·3 to 1·5 gm.; the solutions have a local anaesthetic action. It apparently does not differ in its physiological action from other chlorine narcotics.

The above gives a general indication of the physiological results following the introduction of chlorine into organic substances; the effect of the entrance of this member of the halogen series, as well as bromine and iodine, into other groups, such as the aldehydes and acids, will be described after the discussion of those derivatives.

Esters of Hydrochloric Acid.

Ethyl chloride, C_2H_5Cl, and ethyl bromide have been employed as general anaesthetics; a mixture of these and methyl chloride is known as **somnoform.** Webster (*Biochemical Journal*, June, 1906) investigated these drugs, and also ethyl iodide, which, owing to its unpleasant taste and its volatility, is unsuitable for clinical purposes. There is apparently no difference in the physiological action of these drugs beyond what may be attributed to their varying volatility. With large doses respiration ceases some time before the heart. Blood pressure after a short preliminary rise is considerably depressed, this being due to the depressant action on the cardiac pump. No action on the vagus endings was demonstrated, though Cole (*B. M. J.*, 1903, i, p. 1421) found that the vagus terminations were paralysed. Somnoform appears especially liable to cause respiratory failure.

Ethyl chloride is twice as soluble in blood as in water, and experiments with dogs showed that its vapour has a paralytic action on the heart muscle but that nineteen times as much is required to produce the same effect as chloroform.

Chloroform, $CHCl_3$, is obtained by the action of bleaching powder on dilute alcohol or acetone; the reaction commences in the case of alcohol at 45° C., and the chloroform formed is distilled off, washed with water, treated with concentrated sulphuric acid to destroy other chlorinated derivatives such as those of ethane, and rectified. In all probability alcohol is firstly oxidized to chloral, CCl_3CHO, which, in the presence of calcium hydrate, is converted into chloroform. In the case of acetone, the intermediate product is probably $CCl_3 . CO.CH_3$, which then breaks down into chloroform

and acetic acid. A much purer preparation may be obtained by the action of alkalis on chloral. It is only slightly soluble in water, 1 litre of saturated solution at ordinary temperatures containing about 7 gms. of chloroform. The pure preparation is not very stable, breaking down into the very toxic phosgene, $COCl_2$, hydrochloric acid and chlorine; the official preparation, which is much more stable, contains a trace of ethyl alcohol, or when made from acetone a small quantity of that substance; both these in the amounts present are physiologically inert, and there is no reason why chloroform prepared from ethyl alcohol should in any way be preferred to that obtained from acetone.

Breteau and P. Woog have found that chloroform may be kept in ordinary glass bottles in diffused daylight without suffering decomposition, if any of the following substances are added in proportion of 2–4 parts per 1,000:—Oil of turpentine, pure spermaceti, menthol geraniol, menthol salicylate, and thymol.

The theories as to the narcotic or anaesthetic properties of chloroform have been discussed in the general introduction to the narcotic compounds. The symptoms known as 'delayed chloroform poisoning', which include a remarkable fatty infiltration of the liver and are not infrequently fatal, are in reality those of an acid intoxication. They are occasionally met with after other anaesthetics. Diminished oxidation processes characterize the action of all the halogen narcotics; it is supposed that the imperfect oxidation of the body fats gives rise to acids of the fatty series, and hence the production of these symptoms. The action does not apparently depend on the narcosis, but is a special property of this class of drugs.

Carbon tetrachloride, CCl_4, which was originally investigated by Simpson and others in the early days of anaesthesia, was made the subject of more recent experiment by Marshall, who found that the differences in action between this body and chloroform were mainly due to its physical characters. It is, however, more toxic and more irritating to the mucous membrane of the trachea and bronchi. Recently it has been employed by hairdressers to clean the hair, and a case of accidental poisoning owing to the inhalation of the vapour has been reported (*Lancet*, 1907, i. 1725). This case was apparently serious, and very nearly had a fatal termination.

Dichlorethane, $CH_3 . CHCl_2$, the symmetrical derivative ethylene dichloride, $CH_2Cl.CH_2Cl$, and trichlorethane or methyl chloroform, $CH_3 \cdot CCl_3$, have all a very similar action to chloroform.

Esters of Hydrobromic Acid.

The lower alkyl bromides have a similar action to the chlorides; thus methyl bromide, CH_3Br, and ethyl bromide, C_2H_5Br, have anaesthetic properties, and are only slightly toxic, but the latter substance produces irritation of the respiratory passages to a greater extent than the corresponding chlorine derivative. The narcosis produced by ethyl bromide differs from that of chloroform, since it sets in more rapidly, but also ceases more quickly. This is in agreement with Schleich's theory, according to which narcosis is deeper and lasts longer, the higher the boiling-point of the anaesthetic (boiling-point of ethyl bromide = 38°, chloroform = 61°).

Bromoform, $CHBr_3$, has a narcotic action, and was first used in 1889 by Stepp in whooping-cough of children, and also in cases of asthma. It is prepared from either alcohol or acetone in a very similar manner to chloroform.

In ethylene dibromide, $C_2H_4Br_2$, the toxicity increases; the anaesthetic action is slight, and it tends to cause paralysis of the extremities and stoppage of the heart. It is stated to have a peculiar action on the respiratory centre, diminishing the desire to breathe, and it has consequently been suggested that it might be of advantage in asthma.

The bromine derivatives being less stable than the chlorine decompose more rapidly, and many attempts have been made to employ such compounds in place of potassium bromide in epilepsy, with the hope of avoiding the depressant effects of this salt. Up to the present, however, no substitute has been found; thus hexamethylene-tetramine-brommethylate (**bromalin**), $(CH_2)_6N_4.CH_3Br$, has not the desired effect; the sedative action is much less than that of potassium bromide, as are also the unpleasant after-effects.

Tribromhydrin, $C_3H_5Br_3$, has no advantage over bromide; it reacts very similarly to the corresponding trichlorhydrin. It is also an intestinal irritant.

Bromipin is a compound of bromine with sesame oil (see also Iodipin), which liberates the element slowly in the organism.

The disadvantage of the organic bromine preparations in the treatment of epilepsy is that, although a considerable amount of bromine may be administered, it is present in such a form that only small quantities are set free in the body at a time; consequently, when it is desirable to produce a rapid effect these preparations are useless.

Esters of Hydriodic Acid.

In the iodine derivatives the antiseptic properties are much more marked than in the others, and an increase in toxicity is observed. Ethyl iodide, C_2H_5I, acts like chloroform, but anaesthesia comes on slowly and is more permanent. It may be used to relieve spasms of the respiratory passages.

Iodoform, CHI_3, possesses narcotic and hypnotic properties, but is chiefly characterized by its extraordinary antiseptic power. Partly for this reason, but mainly because the majority of the iodine derivatives employed in medicine are allied to the aromatic phenols, they will be discussed later (see Chap. VIII).

Aromatic Esters of Halogen Acids.

The hydrogen atoms in the benzene nucleus are more readily replaced by chlorine and bromine than the hydrogen of the paraffins. An important method used in their preparation consists in the decomposition of the diazo derivatives (p. 41) by means of the haloid acid; e. g.

$$C_6H_5N:N.OSO_3H + HI = C_6H_5I + N_2 + H_2SO_4,$$

and by the action of heat upon the cuprous salt addition product,

$$C_6H_5N:N.Cl.Cu_2Cl_2 = C_6H_5Cl + N_2 + Cu_2Cl_2.$$

The benzene halogen derivatives have a slight odour, are insoluble in water, volatilize without decomposition, and are very stable. Unlike the aliphatic substitution products, they are unacted upon by the alkalis, ammonia, potassium cyanide, &c.

Corresponding to their stability it is found that the halogen is not split off in the organism, and that they do not show hypnotic properties. With the entrance of chlorine the antiseptic properties increase (see later).

Chlorbenzene acts on the spinal cord to a greater extent than benzene.

The action of brombenzene is more powerful, and

$$C_6H_4\begin{matrix}Br\\CH_3\end{matrix}\ 1:4$$

is very toxic; the entrance of bromine into the molecule of benzene does not bring about narcotic properties.

The aromatic iodo compounds are more toxic than those not containing that halogen.

II. Esters of Nitrous and Nitric Acid.

The nitrous acid esters may be obtained by the action of nitrous acid on the alcohols, e. g.

$$C_2H_5O\!:\!H + OH\!:\!NO = C_2H_5O.NO + H_2O.$$

They are liquids with characteristic smell, and are readily decomposed by alkalis into the corresponding alcohol and alkaline nitrite. They are isomeric with the nitro paraffins, e. g. nitroethane, $C_2H_5NO_2$, but these on reduction yield amines, $C_2H_5NH_2$, whereas the corresponding nitrous ethyl ester is saponified, yielding ethyl alcohol, C_2H_5OH.

The esters of nitric acid result from the interaction of alcohols and nitric acid, e. g.

$$C_2H_5O\!:\!H + OH\!:\!NO_2 = H_2O + C_2H_5O.NO_2.$$

They are pleasant-smelling liquids, exploding when rapidly heated, and easily saponified by alkalis, giving alcohol and alkaline nitrate.

Physiological Properties.

As a general rule, the entrance of the nitro or nitroso group into a molecule increases its toxicity, irrespective of the manner in which the linkage is effected; whether through oxygen as in the esters, or direct to carbon as in nitroso and nitro paraffins.

The nitrous esters of the fatty series do not act on the vasomotor centre but directly on the vessels, causing powerful expansion.

Cash and Dunstan investigated carefully-prepared specimens of nitrous esters. They found that, as regards the principal effect, i. e. reduction of blood pressure, the activity of various nitrites took the following order when equal volumes were administered to animals by inhalation:—(1) Secondary propyl, (2) tertiary butyl, (3) secondary butyl, (4) *iso*-butyl (nearly equal), (5) tertiary amyl, (6) α-amyl, (7) β-amyl (nearly equal), (8) methyl, (9) butyl, (10) ethyl, (11) propyl. This order is somewhat modified when the nitrites are given by intra-vascular injections. When the duration of subnormal pressure is considered, the order is nearly the reverse of that given above; the effect of methyl nitrite being the last, and secondary propyl one of the first to disappear.

In some animals toxic effects in the tissues have been observed, but in man death occurs owing to blood changes, methaemoglobin and nitric oxide haemoglobin being formed.

Divergent views have been held as to the chemical action of the nitrites on the tissue cells; Loew considers that a combination occurs with the amide group of the protein molecule; Marshall, Haldane, and others consider that the nitrous acid esters act directly. Binz considers that nitric oxide is formed; a small portion is excreted unchanged in the urine.

Bradbury investigated:

Methyl nitrate	$CH_3 . ONO_2$
Ethylene dinitrate	$CH_2 . ONO_2$ | $CH_2 . O.NO_2$
Nitroglycerin	$CH_2O.NO_2$ | $CHO.NO_2$ | $CH_2O.NO_2$
Erythrol tetranitrate	CH_2ONO_2 | $(CH.O.NO_2)_2$ | CH_2ONO_2
Mannitol hexanitrate	CH_2ONO_2 | $(CH.ONO_2)_4$ | CH_2ONO_2

Erythrol tetranitrate is less powerful than amyl nitrile or nitroglycerin, but its effects are more prolonged; mannitol hexanitrate is not nearly so powerful, but its action may be more prolonged. Its main advantage is its comparatively low cost.

Marshall found mannitol pentanitrate intermediate in action between the two.

Nitroglycerin is practically absorbed into the blood unchanged, hence its powerful and prolonged action (Brunton).

Nitro Paraffins. When the nitro group is linked directly to carbon, as for instance the nitro paraffins, an entirely different physiological reaction appears. Nitro ethane, $C_2H_5NO_2$, for instance, although a toxic substance, has no action at all on the blood vessels, and, like nitromethane, CH_3NO_2, causes death in relatively small doses.

Nitro Derivatives of Aromatic Series. The introduction of the nitro group into the aromatic series (p. 40) also raises the toxicity

in the resulting substance. Thus nitrobenzene produces tremors and increased reflexes, and eventually coma.

Nitrothiophene acts in a precisely similar manner to nitrobenzene.

Nitronaphthol is toxic in small doses, either given by the mouth or subcutaneously. On the other hand *p*-nitrotoluene,

$$C_6H_4\begin{cases}CH_3\\NO_2\end{cases}$$

is almost non-toxic.

Nitroglycerin, hydroxylamine, and nitrobenzene act chiefly on the central nervous system; the action on the blood is secondary. The chief toxic action of dinitrobenzene is on the red blood cells.

The entrance of a negative group causes a decrease or entire loss of toxic properties, as, for instance, in the case of nitrobenzoic acids or nitrobenzaldehydes, which are converted into acids (p. 77) in the body.

III. Esters of Sulphurous and Sulphuric Acids.

When silver sulphite is acted upon by ethyliodide, the ethyl ester of sulphurous acid results,

$$Ag.SO_2OAg + 2C_2H_5I = 2AgI + C_2H_5.SO_2OC_2H_5.$$

Such esters may be regarded as the derivatives of unsymmetrical sulphurous acid; they are decomposed by potash with the formation of ethyl sulphonic acid,

$$C_2H_5SO_2OC_2H_5 + H_2O = C_2H_5SO_2OH + C_2H_5OH.$$

In the aromatic series the corresponding sulphonic acids are of very much greater importance, and are formed by the direct action of sulphuric acid upon the benzene derivatives,

$$C_6H_5.H + OH.SO_2OH = H_2O + C_6H_5.SO_2OH.$$

This method of introducing the sulphonic acid group can be used with a very large number of substituted aromatic derivatives, and gives rise to a group of substances soluble in water or whose sodium salt is soluble in that liquid, a factor of importance in the dye industry.

The interaction of sulphuric acid and the alcohols gives rise to esters which are much less stable than the sulphonic acids. Ethyl alcohol gives the ethyl ester of sulphuric acid

$$SO_2\begin{cases}OC_2H_5\\OH\end{cases}$$

Phenol gives the ester

$$SO_2\langle^{OC_6H_5}_{OH}$$

Unlike the previously mentioned derivatives, the hydrocarbon radical is attached to oxygen, and in consequence they are readily decomposed by alkalis, regenerating acid and alcohol.

The introduction of these acidic groupings into organic substances results in a great drop in pharmacological activity, thus the toxic phenol gives the inert phenol sulphonic acid,

$$C_6H_4\langle^{OH}_{SO_2OH}$$

or the equally inert phenyl sulphuric ester (see p. 56),

$$SO_2\langle^{OC_6H_5}_{OH}$$

The hypnotic properties of morphia are modified and considerably weakened in its sulphuric ester.

Phenyl-dimethyl-pyrazol is toxic, whereas its sulphonic acid derivative given in doses of 5–6 gms. to rabbits produces no effect.

Dinitro-naphthol is toxic in small doses, whereas its sulphonic acid is inert.

It is interesting to note in this connexion Ehrlich's observation that basic dyes stain the cortical nerve cells, whereas their sulphonic acids do not.

B. THE ETHERS.

The ethers are derivatives of the alcohols in which the hydrogen of the hydroxyl group is replaced by alkyls, or they may be regarded as derivatives of water in which both hydrogen atoms have been replaced by similar or dissimilar groups; they are consequently classified as simple, such as ethyl ether, $C_2H_5.O.C_2H_5$; or mixed, such as methyl ethyl ether, $CH_3.O.C_2H_5$.

1. Their most important method of preparation consists in the interaction of sulphuric acid and the alcohols. Thus

A. $$SO_2\langle^{OH}_{OH} + C_2H_5OH = SO_2\langle^{OC_2H_5}_{OH} + H_2O$$

The ethyl ester of sulphuric acid.

B. $$SO_2\langle^{OC_2H_5}_{OH} + C_2H_5OH = SO_2\langle^{OH}_{OH} + C_2H_5.O.C_2H_5$$

or at this stage a different alcohol may be allowed to react with the sulphuric ester and a mixed ether obtained thus

$$SO_2\begin{matrix}OC_2H_5\\OH\end{matrix} + CH_3OH = SO_2\begin{matrix}OH\\OH\end{matrix} + C_2H_5.O.CH_3.$$

The ethers are volatile, neutral liquids, only slightly soluble in water. The lowest members are gases, the next liquids, and the highest solids; their boiling-points are much lower than those of the corresponding alcohols. From a chemical standpoint they show but slight reactivity, since all the hydrogen atoms are attached to carbon. Although not easily attacked by oxidizing agents, they yield, when oxidized, the same products as their corresponding alcohols.

Physiological Properties.

The replacement of hydrogen in the hydroxyl group of the alcohols results in the formation of substances much more stable towards the oxidation processes of the body. The lower volatile members of the series are more used as anaesthetics than hypnotics. Dimethyl ether, $(CH_3)_2O$, acts very like nitrous oxide, producing a rapid and transient anaesthesia.

The anaesthetic properties of diethyl ether, $(C_2H_5)_2O$, are well known. Its action is discussed in the general introduction to the narcotic bodies.

The mixed aliphatic ethers have not been investigated, and it would be of considerable interest to find out whether methyl ethyl ether, $CH_3.O.C_2H_5$, which in the pure state boils at 11° C., has any advantages over ordinary diethyl ether.

As the molecular magnitude of the ethers increases, their physiological reaction becomes less.

Methylal, $CH_2(OC_2H_3)_2$, produces anaesthesia slowly; the action is prolonged and deep but somewhat uncertain, and patients quickly become accustomed to it.

Acetal, $CH_3CH(OC_2H_5)_2$, is also an uncertain hypnotic, and produces unpleasant cardiac symptoms and considerable excitement.

The mixed aromatic aliphatic ethers, such for instance as phenetol, $C_6H_5.O.C_2H_5$, are not comparable to the simple aliphatic ethers, and the derivative mentioned is entirely without anaesthetic action.

CHAPTER V

THE ALCOHOLS AND THEIR DERIVATIVES (continued). The chemical and physiological characteristics of the Aldehydes, Ketones, Sulphones, Acids. The derivatives of the Acids. Halogen substitution products, Esters, Amides, Nitriles. Sulphur derivatives.

THE OXIDATION PRODUCTS OF THE ALCOHOLS.

I. THE ALDEHYDES.

THE aldehydes are the first oxidation products of the primary alcohols, and contain the group (CHO)′ linked on to an organic radical.

They may be obtained :—

1. By the oxidation of the primary alcohol, which readily takes place on warming them with potassium bichromate and sulphuric acid,

$$CH_3.CH_2OH \rightarrow CH_3.C\langle^{H}_{O}$$

or

$$C_6H_5CH_2OH \rightarrow C_6H_5.CHO$$

Benzyl alcohol. Benzaldehyde.

2. Aldehydes of both aliphatic and aromatic series are obtained by the distillation of the lime salts of the respective acids with calcium formate,

$$(CH_3COO)_2Ca + (H.COO)_2Ca = 2CaCO_3 + 2CH_3COH$$

or $(C_6H_5COO)_2Ca + (H.COO)_2Ca = 2CaCO_3 + 2C_6H_5COH.$

3. Aldehydes of the aromatic series are obtained by the action of chromyl chloride, CrO_2Cl_2, upon the homologous benzenes. Thus toluene gives firstly a brown addition product, $C_6H_5CH_3.(CrO_2Cl_2)_2$, which is decomposed into benzaldehyde, $C_6H_5.CHO$, by the action of water.

The aldehydes exhibit the usual physical properties of an homologous series : the lower are volatile liquids soluble in water, but as the molecular magnitude increases, their solubility in that medium becomes less and eventually nil, and at the same time they decompose

on distillation at ordinary pressures. In chemical respects they are neutral substances characterized by their great reactivity. They readily pass to carboxylic acids, and in consequence are powerful reducing agents—the aliphatic to a greater extent than the aromatic:

$$CH_3.CHO + O = CH_3COOH$$
$$C_6H_5CHO + O = C_6H_5COOH.$$

The majority of the aliphatic aldehydes are converted into resins by the alkalis, but those of the aromatic series give rise to a mixture of acid and alcohol, e.g.

$$2C_6H_5CHO + KOH = C_6H_5COOK + C_6H_5CH_2OH.$$

On reduction they yield primary alcohols:

$$R.CHO + 2H = R.CH_2OH.$$

Under ordinary circumstances they do not unite with water, but many of their halogen substitution products yield readily-decomposable hydrates; e.g. chloral, $CCl_3.CHO$, gives chloral hydrate,

$$CCl_3.CH\begin{matrix}OH\\OH\end{matrix}$$

They unite with prussic acid, forming the nitriles of the hydroxy acids, e.g.

$$CH_3CHO + HCN = CH_3.CH\begin{matrix}OH\\CN\end{matrix}$$

Nitrile of lactic acid.

$$C_6H_5CHO + HCN = C_6H_5.CH\begin{matrix}OH\\CN\end{matrix}$$

Nitrile of mandelic acid.

Similarly they combine with sodium bisulphite, forming crystalline derivatives that may be employed for their purification—

$$CH_3CHO + SO\begin{matrix}ONa\\OH\end{matrix} = CH_3.CH\begin{matrix}OH\\SO_2ONa.\end{matrix}$$

With ammonia the aliphatic aldehydes also form compounds which may be similarly employed for their purification,

$$CH_3CHO + NH_3 = CH_3.CH\begin{matrix}OH\\NH_2\end{matrix}$$

but with the aromatic amines a more complicated reaction occurs. Aldehydes of both series combine with phenylhydrazine and hydroxylamine,

$$R.CHO + H_2N.NHC_6H_5 = R.CH:N.NHC_6H_5 + H_2O$$

or

$$RCHO + H_2N.OH = RCH:N.OH + H_2O.$$

The lower members of the aliphatic series readily polymerize, formic aldehyde, for instance, changes slowly at 20°, but rapidly at ordinary temperatures, to trioxymethylene, $(H.CHO)_3$. Small quantities of acids convert acetaldehyde, CH_3CHO, at ordinary temperatures into paraldehyde, $(CH_3CHO)_3$, but if the temperature be kept low metaldehyde, $(CH_3CHO)_3$, is formed.

The aromatic aldehydes are distinguished from those of the other series by not undergoing such molecular condensations, i.e. by not polymerizing.

Physiological Characteristics.

The physiological characteristics of the alkyl group, observed in this class of derivatives, are probably more marked owing to the great chemical reactivity of the CHO group. In formaldehyde, the effect on the tissues and cells as well as its great antiseptic properties are prominent characteristics. But in acetaldehyde, CH_3CHO, the anaesthetic properties are more marked, and still more pronounced in its polymeric form paraldehyde, which is not so toxic as metaldehyde.

The entrance of hydroxyl groups into the aldehyde molecule depresses their physiological reactivity, and the aldose sugars, for instance, show no trace of narcotic properties.

The aromatic aldehydes are only slightly toxic, owing to the ease with which they are oxidized, and their physiological properties are practically those of the corresponding aromatic acid.

The strong antiseptic action and hardening effects of formaldehyde on the tissues are closely related to its exceptional reactivity. Owing to this reactivity various compounds can be obtained, and it is necessary from a physiological standpoint that these should slowly break down with the liberation of formaldehyde.

Such substances are the compounds resulting from the interaction of formaldehyde and gelatine, starch, dextrine, and milk-sugar. They are for the most part very mild antiseptics.

Formaldehyde is not usually given internally. Recently, tablets known as **formamint** have been introdueed, in which the formic aldehyde is combined with milk-sugar, and liberated on solution. They are intended for the treatment of septic conditions in the mouth and fauces. Maguire, in 1900, described a method of injecting a 1 in 2,000 solution of formic aldehyde into the median basilic vein for the disinfection of the lungs in phthisis, but although he reported good results there is no evidence that an

antiseptic of sufficient strength can be employed in this manner without producing toxic symptoms. Experiments *ad hoc* by one of the present writers will be found in the Guy's Hospital *Reports*, vol. lviii. Recently, formic acid and the formates have been credited with tonic properties, but the clinical evidence is as yet meagre.

The formyl compound of urea, $CO(N:CH_2)_2$, which slowly breaks off formaldehyde and possesses no smell, has been introduced.

Compounds have also been formed between formaldehyde and the antiseptic group of phenols, such as eugenol, thymol, and iodo thymol; these readily break down into their components, and a combined action of antiseptic substances is obtained.

When ammonia acts on formaldehyde, hexamethylene tetramine results. This also in all probability liberates formaldehyde in the body, and to this may be ascribed its value as a urinary antiseptic; it limits suppuration anywhere along the urinary tract from the kidneys to the orifice of the urethra, and on this account is the best urinary antiseptic we possess. It goes by a number of trade names, namely, **urotropine, aminoform, formin, cystamine, cystogen, metramine, uretone, urisol,** and **vesaloine.**

Paraldehyde, a polymeric form of acetaldehyde, has the disadvantage of a very unpleasant odour and taste. It acts first on the higher cerebral centres and then on other parts of the central nervous system, finally producing spinal anaesthesia and death. It has no depressant action on the heart (cf. chloral), and it may be given for long periods with safety. Its main disadvantage is its irritant action on the gastric mucosa. It has antiseptic powers, like acetaldehyde, and can be combined with starch, dextrine, &c., to form antiseptic applications.

Physiological Characteristics of Halogen Substitution Products of the Aldehydes.

The entrance of chlorine into acetaldehyde with the formation of trichloracetaldehyde or chloral, $CCl_3.CHO$, causes a large increase in narcotic power, but the simultaneous action of the halogen is observed, viz., depression of cardiac and respiratory centres.

That the action of chloral is due to both halogen and aldehyde groups is seen by the fact that on oxidation to trichloracetic acid, $CCl_3.COOH$, the physiological reaction disappears, whereas on reduction to trichlorethyl alcohol, $CCl_3.CH_2OH$, a substance with narcotic properties is obtained, although these are much

less powerful than those of the original chloral. The action of the chlorine may be traced by comparing chloral with paraldehyde, since the latter has no depressant action on cardiac and respiratory activity, and indeed is said to act as a mild cardiac tonic.

Chloral, CCl_3CHO, was discovered in 1832 by Liebig, and is obtained by the action of chlorine upon alcohol; the reaction is complicated, and will be found discussed in works on organic chemistry. It is an oily, pungent-smelling liquid, which polymerizes on keeping. Unlike acetaldehyde it combines with water, forming a crystalline derivative,

$$CCl_3CH\begin{matrix}OH\\OH\end{matrix}$$

chloral hydrate, a substance which, contrary to the general rule, contains two hydroxyl groups linked into one carbon atom. It readily yields chloroform with even dilute solutions of alkali, $CCl_3.CHO + KOH = CHCl_3 + H.COOK$, and it was this that led Liebreich in 1869 to try its hypnotic action, since it might be supposed that this decomposition would take place in the body; it was, however, shown later that chloral is reduced to trichlorethyl alcohol, CCl_3COH, and is eliminated as a derivative of this substance and glycuronic acid (see p. 60); consequently the old idea of its physiological reaction had to be abandoned.

Butyl chloral, $CCl_3.CH_2.CHO$, has a more powerful action than chloral, but the effects pass off more rapidly. Butyl chloral hydrate is said not to depress the heart, but this is by no means certain. There is no explanation for its specific effect on the fifth nerve. **Trigemin** is a compound of butyl chloral hydrate and pyramidon.

The corresponding brom and iodo substitution products of acetaldehyde show very considerably diminished hypnotic action.

Bromal, $CBr_3.CH(OH)_2$, in animals causes irritation of the respiratory passages, and in larger doses dyspnoea and cyanosis; still larger doses produce anaesthesia but not hypnosis.

Iodal, $CI_3.CH(OH)_2$. The replacement of bromine by iodine appears to increase the action upon peripheral nerve-endings and muscles, but the substance has only slight hypnotic properties. The mono-iodo derivative $CH_2I.CH(OH)_2$ has not such a powerful action as chloral, but has a strong depressant action on the heart.

Owing to the reactivity of the aldehyde grouping in chloral it is possible to modify the substance in various directions; up to the present it has been found that all those derivatives which easily split off chloral in the organism show the ordinary chloral reaction,

whereas the more stable either do not possess hypnotic properties or are toxic substances. Combinations with other hypnotics have not given any very striking results, thus chloral alcoholate,

$$CCl_3.CH\begin{matrix}OH\\OC_2H_5\end{matrix},$$

formed by the addition of chloral and alcohol has no advantages over the hydrate itself.

Dormiol, introduced by Fuchs, and formed by the union of chloral and amyl alcohol,

$$CCl_3.CHO + OH-C\begin{matrix}CH_3\\CH_3\\C_2H_5\end{matrix} = CCl_3.CH\begin{matrix}OH\\O-C\end{matrix}\begin{matrix}CH_3\\CH_3\\C_2H_5\end{matrix}$$

is not very stable, being easily broken down, probably even by solution in water, into its constituents. It has a penetrating smell and taste, and its action is not reliable.

Chloral urethane (**ural, somnal**),

$$CCl_3.CH\begin{matrix}OH\\NH.COOC_2H_5\end{matrix},$$

was prepared in the hope that the hypnotic effects of ethyl urethane might be added on to that of chloral. An apparently identical body is known as **uralium.** The hypnotic effect wears off before the toxic, and in animals paralysis of the hindquarters accompanies the sleep induced by the drug. Diarrhoea, diuresis, salivation, itching, and disturbances of respiration are produced by large doses.

Similarly, chloral was combined with acetone, which has a slight narcotic action, but the resulting substance, chloral acetone,

$$CCl_3.CHOH.CH_2.CO.CH_3,$$

possesses but little narcotic action, and in the organism is dehydrated with formation of $CCl_3.CH:CH.CO.CH_3$. On the other hand the corresponding aromatic derivative chloral acetophenone, $CCl_3.CH.OH.CH_2.CO.C_6H_5$ (the combination with acetophenone, a powerful hypnotic), has not the slightest hypnotic action, but like the previous compound it is eliminated as

$$CCl_3.CH:CH.CO.C_6H_5.$$

Then, in another direction, Mering and Zuntz introduced the compound of formamide and chloral, **chloral formamide,** or **chloral amide.** This is formed by the direct union of the two,

$$CCl_3.CHO + H.CONH_2 = CCl_3.CH\begin{matrix}OH\\NH.OCH\end{matrix}$$

a reaction which does not take place with the unsubstituted acetaldehyde. This derivative has a slightly bitter taste, less harmful action than chloral, but on the other hand much less hypnotic power. Since urochloralic acid is found in the urine, its action probably depends on its slow decomposition in the organism into chloral itself.

Chloral ammonia,

$$CCl_3 . CH\langle^{OH}_{NH_2},$$

was intended to combine the hypnotic action of chloral hydrate with the stimulant action of ammonia on the heart and respiration.

The condensation products of chloral with various aldoximes and ketoximes have given products of no pharmacological value. These derivatives, formed according to the general reaction

$$R : N.OH + CCl_3 . CHO = C.Cl_3 . CH\langle^{OH}_{ON : R}$$

are but slightly soluble in water.

The products resulting from the condensation of chloral with various sugars have been investigated by Hauriot and Richet, and others.

Milk-sugar chloralide has no narcotic action, but produces epileptiform fits with bronchorrhoea and asphyxia.

Chloral (free from water) and glucose are combined as **chloralose**, $C_8H_{11}Cl_3O_6$. It is a somewhat rapid hypnotic, but is less easily tolerated than chloral hydrate. It may produce restlessness, diplopia, tremors, and haemoglobinuria. Its main toxic action is on the respiratory centre. Richet says it acts on the grey matter of the cortex cerebri, the cord being unaffected. The uncertain results are said to be due to the formation of a second compound, parachloralose, which is toxic without being hypnotic.

Arabino-chloralose is easily soluble in water, produces no stage of excitement, and has a minimum lethal dose equal to twice that of chloralose. It is, however, a much less powerful hypnotic. A second compound, pararabino-chloralose, is only slightly soluble. The pentose compounds are probably less active and less toxic owing to their greater stability in the body.

When chloral reacts with antipyrine several substances result—hypnal, $C_{13}H_{15}N_2O_3Cl_3$, melting at 67°–68°, and chloralantipyrin, $C_{13}H_{13}Cl_3N_2O_2$, formed at a higher temperature and possessing no physiological reaction. **Hypnal** has a similar toxic and hypnotic action to chloral hydrate. The toxic dose is the same, so that the

presence of antipyrin heightens the toxicity of the chloral. It is used as an analgesic as well as a hypnotic.

The various condensation products of chloral with aromatic hypnotics, investigated by Tappeiner, have little or no physiological reaction.

II. THE KETONES.

The ketones are a group of substances closely related to the aldehydes, both contain the carbonyl group linked, in the case of the former compounds, to alkyl group, but in the case of aldehydes to an alkyl group and hydrogen.

$$\begin{array}{l} CH_3 \\ | \\ CO \\ | \\ CH_3 \end{array}$$ Dimethyl ketone, $$\begin{array}{l} CH_3 \\ | \\ CO \\ | \\ H \end{array}$$ Acetaldehyde.

The relationships will be noticed in their more important methods of preparation and general reactions. They may be divided into two classes, in a similar manner to the ethers: Simple, such as acetone, $CH_3.CO.CH_3$; and Mixed, such as methyl ethyl ketone, $CH_3.CO.C_2H_5$.

They are formed by the oxidation of secondary alcohols,

$$CH_3.CHOH.CH_3 \rightarrow CH_3.CO.CH_3$$
Iso-propyl alcohol.

$$C_6H_5.CHOH.CH_3 \rightarrow C_6H_5.CO.CH_3$$
Phenylmethyl carbinol. Acetophenone.

or by the distillation of the lime-salt of the corresponding acid,

$$(CH_3COO)_2Ca = CaCO_3 + CH_3COCH_3$$
$$(C_6H_5COO)_2Ca = CaCO_3 + C_6H_5.CO.C_6H_5$$

whereas the mixed ketones are obtained from the lime-salt of two acids,

$$(CH_3COO)_2Ca + (C_2H_5COO)_2Ca = 2CH_3.CO.C_2H_5 + CaCO_3$$
$$(C_6H_5COO)_2Ca + (CH_3COO)_2Ca = 2C_6H_5COCH_3 + 2CaCO_3.$$

The ketones are neutral bodies, and the lower members of the series are volatile etherial-smelling liquids. They are much less readily oxidized than the aldehydes, and unlike that group of substances polymerize.

Their reactions with hydroxylamine, phenylhydrazine, and prussic acid resemble very closely those of the previous group,

$$(CH_3)_2CO + H_2N.NHC_6H_5 = (CH_3)_2C:N.NHC_6H_5 + H_2O$$

$$C_6H_5CO.CH_3 + H_2N.OH = C_6H_5.C(N.OH).CH_3$$

$$CH_3.CO.CH_3 + HCN = CH_3C\begin{matrix}OH\\CH_3\\CN\end{matrix}$$

Those containing a methyl group react with sodium bisulphite, forming crystalline derivatives which may be employed for purification owing to the ease with which they are obtained, and then decomposed by acids or alkalis with the recovery of the ketone.

$$CH_3.CO.CH_3 + NaHSO_3 = (CH_3)_2C\begin{matrix}OH\\SO_2ONa\end{matrix}$$

and

$$(CH_3)_2C\begin{matrix}OH\\SO_2ONa\end{matrix} + NaOH = (CH_3)_2CO + Na_2SO_3 + H_2O.$$

Physiological Characteristics.

The ketones in general physiological action closely resemble the alcohols, they give rise to narcosis and lowering of the blood pressure. Acetone, $CH_3.CO.CH_3$, produces intoxication and sleep, but is less powerful than ether or chloroform and less toxic than ethyl alcohol. The hypnotic properties, traceable to the ethyl groups, are clearly seen in diethyl ketone, $C_2H_5.CO.C_2H_5$ (**Propion**), which was introduced as a hypnotic and anaesthetic, but its solubility in water is not great, and this, combined with an unpleasant taste, renders it of little use.

Similar hypnotic properties are noticed in dipropyl ketone, but as the molecular magnitude increases the solubility in water decreases, and the higher ketones are not likely to be of any pharmacological value.

The diminution in physiological action which accompanies the introduction of hydroxyl groups is observed in the case of the inert ketoses (ketone sugars) just as it is in that of the aldehydes.

The stability of the ketonic acids depends on the relative positions of the ketonic and carboxyl groupings. Thus acetoacetic ester, $CH_3CO.CH_2.COOH$, is very unstable, readily breaking down into acetone.

Levulinic acid, $CH_3COCH_2CH_2.COOH$, on the other hand, is more stable, and at the same time much more toxic.

Ketones, both simple and mixed, aliphatic and aromatic, are observed to possess hypnotic properties. Benzophenone, $C_6H_5.COC_6H_5$, has a slight action but much less than the aliphatic derivatives. In the mixed aromatic and aliphatic ketones the action depends largely on the nature of the latter radical. Thus acetophenone, $C_6H_5CO.CH_3$ (**Hypnone**), has a marked hypnotic action.

The attempts which have been made to increase the solubility of acetophenone by the introduction of the amido group or its substituted derivatives have not led to substances of practical importance.

Phenyl ethyl ketone, $C_6H_5COC_2H_5$, has a more powerful action than acetophenone.

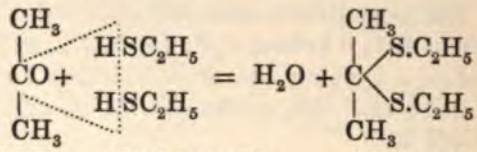
DERIVATIVES OF THE KETONES.

SULPHONALS.

When water is withdrawn from a mixture of alcohol and aldehyde, the acetals result,

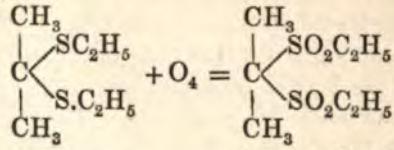
$$CH_3CHO + 2C_2H_5OH = CH_3CH(OC_2H_5)_2 + H_2O,$$

but a corresponding reaction does not take place with the ketones. The corresponding sulphur derivatives, however, are known, and are obtained by the action of a dehydrating agent, such as hydrochloric acid on a mixture of ketone and thioalcohol,



Acetone. Ethyl mercaptan. Acetone-ethyl mercaptol.

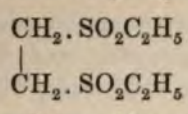
The resulting substances are liquids with an unpleasant smell, and are readily oxidized by potassium permanganate to a group of substances called sulphones,



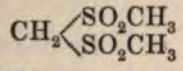
Acetone-diethyl sulphone.

Many of these derivatives, investigated by Baumann and Kast, have valuable hypnotic properties.

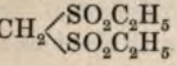
They found the disulphones containing sulpho groups joined to separate carbon atoms, for instance, ethylene-diethyl sulphone,



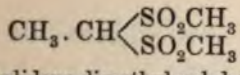
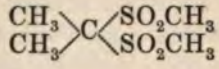
had no physiological reaction. Also, that disulphones derived from methane were without action, as, for instance, methylene-dimethyl sulphone,



or methylene-diethyl sulphone,

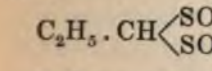


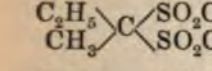
When hydrogen in the original methane of the methylene-dimethyl sulphones was substituted by methyl again, inert substances resulted,

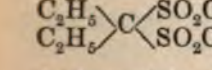
 or 

Ethylidene-dimethyl sulphone.

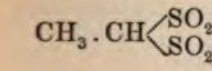
But with the entrance of ethyl groups narcotic properties followed; thus

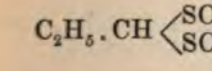
 has a slight narcotic action;

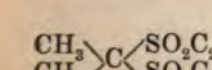
 has a slight narcotic action;

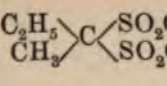
 is isomeric with, and has precisely the same action as, sulphonal.

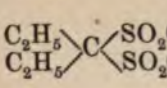
And precisely corresponding physiological reactions are observed in the derivatives of methylene-diethyl sulphone; thus

 has a similar action to sulphonal.

 produces sleep and has toxic properties.

 (**Sulphonal**) in small doses is excreted unchanged in urine and produces sleep; in large doses it produces inco-ordination, and a condition resembling drunkenness.


(**Trional**) has a more powerful and prolonged action than sulphonal.


(**Tetronal**) is much less soluble than the other compounds and has the most powerful hypnotic action of all the sulphones.

The intensity of the action of these sulphones is consequently dependent on the number of ethyl groups they contain: this, apparently, is only true for dogs. Clinically, the distinction does not hold good.

Sulphonal and trional are only slightly soluble in water, and hence are but slowly absorbed; consequently, their action tends to be unduly prolonged; also the use of these substances, if continued for a long time, may bring about destructive action on the red blood corpuscles and consequent haematoporphyrinuria.

To increase the solubility of these derivatives, attempts have been made to produce pharmacologically active amido substitution products, but so far without success.

As regards the metabolic changes of the sulphones, the interesting observation has been made that those which are most stable outside the body are physiologically reactive, and are to a greater or less extent broken down by the organism, whereas those that are least stable are inert, and pass through unchanged. Thus, of the previously mentioned substances, ethylene-diethyl sulphone, methylene-diethyl sulphone (easily decomposed by alcoholic potash), methylene-dimethyl sulphone, ethylidene-dimethyl sulphone are found unaltered in the urine; whereas sulphonal, 'reversed' sulphonal, trional, and tetronal (substances unacted upon by acids and alkalis, and most oxidizing and reducing agents) are to a varying extent decomposed.

It is, however, true that sulphonals, which are but slightly stable, and hence readily decomposed in the body, may have no hypnotic action. Thus the diethyl sulphone prepared from acetoacetic ester,

$$CH_3 . C(SO_2C_2H_5)_2 . CH_2 . COOC_2H_5,$$

has no hypnotic action, although no trace of it can be found in the urine, and the same is true of its ethyl derivative,

$$CH_3 . C(SO_2C_2H_5)_2 . CH(C_2H_5).COOC_2H_5,$$

in spite of the number of ethyl groups.

III. THE ACIDS.

The organic acids are characterized by the presence of the so-called carboxyl group .COOH and their basicity determined by the number of these present. The acids of the paraffin series are termed fatty, owing to the occurrence of their higher members in the natural fats; these substances, on boiling with alkalis, give rise to glycerin and the corresponding alkali salts—soaps; and hence the process of converting an ester into an acid and alcohol has been termed saponification.

Methods of Preparation.

The most important general methods of preparation are :—

1. The oxidation of the primary alcohols and aldehydes,

$$CH_3.CH_2OH \rightarrow CH_3.COOH$$
$$CH_3.CHO \rightarrow CH_3COOH$$

and in the aromatic series,

$$C_6H_5CH_2OH \rightarrow C_6H_5COOH$$
$$C_6H_5COH \rightarrow C_6H_5COOH.$$

2. The addition of water to the nitriles, often carried out by treatment with 50 per cent. sulphuric acid and water. Or the reaction may be effected by means of alkalis,

$$CH_3CN + 2H_2O + HCl = CH_3COOH + NH_4Cl$$
$$C_6H_5CN + 2H_2O + HCl = C_6H_5COOH + NH_4Cl$$
$$CH_3.CH_2CN + H_2O + KOH = CH_3CH_2COOK + NH_3$$

3. The aromatic monocarboxylic acids are readily obtained from the benzene homologues by oxidation (see p. 42) (other methods will be mentioned later),

$$C_6H_5CH_3 + 3O = C_6H_5COOH + H_2O$$
Toluene.

$$O.C_6H_4(CH_3)_2 \rightarrow C_6H_4(COOH)_2$$
o-Xylene. Phthalic acid.

The lower members of the fatty series are soluble in water, but this property rapidly decreases with increasing molecular weight. The lower may be distilled without change, but the higher members are decomposed. As the molecular magnitude increases the acidity diminishes.

The aromatic acids are found (partly in the free state) in many

balsams and resins, and in the animal organism; they result from the decomposition of albuminous substances, and are crystalline solids which generally sublime undecomposed, and are only soluble with difficulty in water.

Physiological Properties.

The entrance of the acidic carboxyl group into the members of the limit hydrocarbons, resulting in the formation of the acids, gives rise to a class of substances with but slight toxic action. The first member, formic acid, is exceptional, as it is in most of its chemical characteristics. Thus, unlike acetic acid, it is a powerful reducing agent, to which, probably, its antiseptic action may be partly ascribed, and, unlike the other members of the series, it forms no acid chloride, and its nitrile, prussic acid, (HCN), has acidic properties; it is, further, a much more powerful acid than acetic.

Of the fatty series, formic acid has the most powerful antiseptic properties, acetic less, propionic acid least; on the other hand, the corresponding action of the benzene substituted acids increases with increase of molecular weight. Thus phenylacetic acid,

$$C_6H_5CH_2COOH,$$

is less powerful than phenylpropionic, $C_6H_5.CH_2.CH_2.COOH$, and this less than phenylbutyric acid, $C_6H_5CH_2.CH_2.CH_2.COOH$.

Formic acid is much more toxic than the other members of the series, except butyric acid, which has also slight narcotic properties.

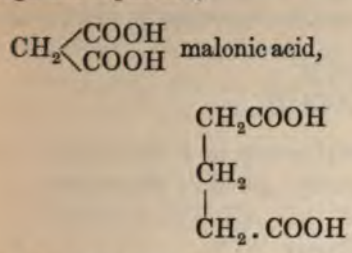
The introduction of the hydroxyl group into butyric acid, resulting in the formation of β-oxybutyric acid, $CH_3.\overset{*}{C}HOH.CH_2.COOH$, gives rise to a substance which exists in three optical isomerides, ascribed to the presence of an asymmetric carbon atom marked with a star; the inactive acid has no physiological action, but the other modifications produce acid intoxication similar to that seen in diabetic coma.

In a very similar manner intraperitoneal injections of the various optical modifications of tartaric acid show that the *laevo*-rotatory acid is the most toxic, the *dextro* acid about one-half, whereas racemic acid is not more than one-quarter as toxic as the *laevo* form.

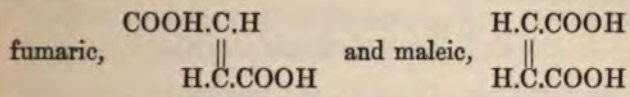
With the dibasic acids the simplest, oxalic,

$$\begin{array}{l} COOH \\ | \\ COOH, \end{array}$$

is toxic, but the toxicity very rapidly decreases as the carboxyl groups are separated,

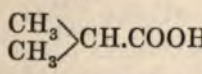


In the unsaturated acids,

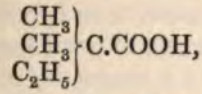


the difference due to structural form is very marked. Fodera showed that the former was non-toxic, whereas the latter was poisonous for higher animals.

The acids of the fatty series, probably owing to the presence of the carboxyl group, do not show narcotic properties, or do not show them to any marked extent. Butyric acid has a slight action which may be traced to the ethyl group, $C_2H_5 . CH.COOH$; it is more marked in dimethyl-acetic acid,

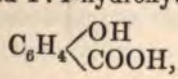


and still more in dimethylethylacetic acid,



of which 3·5 gms. produce sleep and 4·5 sleep and death (rabbits).

The introduction of the carboxyl group *into aromatic substances* is of great pharmacological importance, since a drop in toxicity results. Thus benzene may not be taken in doses of more than 2 to 8 gms. per day, whereas benzoic acid, C_6H_5COOH, is very much less toxic, and may be taken in doses of 12 to 16 gms. Naphthalene in large doses is toxic; its carboxylic acid has no physiological reaction. Not more than 1 to 2 gms. of phenol can be administered, but 1 : 3- and 1 : 4-hydroxybenzoic acid,



have no action, and salicylic acid, the 1 : 2 derivative, may be given in doses twice to three times as great as those of phenol without toxic symptoms appearing. The toxic aniline becomes the inert *m*-amido benzoic acid,

$$C_6H_4\begin{cases}NH_2\\COOH,\end{cases}$$

by the introduction of the carboxyl group into the nucleus. The replacement of hydrogen in the methyl group in phenacetin,

$$C_6H_4\begin{cases}OC_2H_5\\NH.COCH_3\end{cases}\ 1:4,$$

with the formation of

$$C_6H_4\begin{cases}OC_2H_5\\NH.CO.CH_2.COOH\end{cases}$$

brings about the loss of its toxic and therapeutic properties.

Allusion may be made here to the **introduction of the acid radical** of either series into physiologically active basic bodies. The radical of acetic acid, or acetyl, $(CH_3CO)'$, of lactic acid, or lactyl,

$$(CH_3.CH\begin{cases}OH\\CO\end{cases})',$$

benzoic acid, or benzoyl, $(C_6H_5.CO)'$, salicylic acid, or salicyl,

$$(C_6H_4\begin{cases}OH\\CO\end{cases})',$$

&c., can readily replace the hydrogen of the amido or imido group through the interaction of the acid itself or the corresponding acid chloride with the base in question (see pp. 36, 43).

The resulting substances are of great importance in the synthetic preparation of drugs; from a chemical standpoint such derivatives are more stable, and less readily oxidized than the bases from which they are obtained. The lactyl substitution products are more soluble than the acetyl, and the salicyl least; and the latter are broken down with such difficulty by the organism that, as a general rule, they do not possess physiological action. The pharmacological reaction of this group of substances is that of the base from which they are obtained.

The action of the benzoyl residue when introduced into the alkaloids is remarkable; thus ecgonine-methyl-ester (see p. 259) has no anaesthetic action, but its benzoyl derivative, i. e. cocaine, possesses most powerful properties.

The toxicity of aconitine stands in intimate relationship to the benzoyl and acetyl groups present in that alkaloid; when these are eliminated the resulting substance has no action. Even splitting off the acetyl residue causes a drop in toxicity, and the loss of the stimulating action, shown by aconitine, on the respiratory centres.

DERIVATIVES OF THE ORGANIC ACIDS.

A. Halogen Substitution Products.

The halogen derivatives of the fatty acids may be obtained, like the parent acids, by the oxidation of chlorinated alcohols or aldehydes,

$$\underset{\text{Chloral.}}{CCl_3.CHO} \longrightarrow \underset{\text{Trichloracetic acid.}}{CCl_3.COOH}$$

or by the direct substitution of the hydrogen of the hydrocarbon residue by halogens.

These derivatives have more pronounced acidic properties than the acids from which they are derived, otherwise they show very similar characteristics.

Physiological Action.

The replacement of hydrogen by the halogens, as previously noticed in other cases, causes an increase in narcotic action; thus sodium acetate is quite inert, but sodium monochlor acetate, $CH_2Cl.COONa$, has pronounced narcotic properties; the further replacement of hydrogen, instead of increasing this characteristic, brings about a diminution. Dichloracetic acid has less action than the mono derivative, whereas trichloracetic acid, $CCl_3.COOH$, has very slight, if any, corresponding physiological reaction. In this case the difference in the action may be ascribed to the varying stability of the substances. Monochloracetic is easily decomposed on heating, even at body temperature; trichlor is most stable, and dichloracetic of intermediate stability. It is possible that the narcotic action of the first two acids is due to the liberation of hydrochloric acid in the cerebral cortex, since in animals rendered drowsy by these acids the symptoms are diminished by the injection of sodium carbonate into the vessels. Also, trichloracetic acid does not give rise to hydrochloric acid on decomposition, but to chloroform, and, as already stated, has no narcotic action.

have no action, and salicylic acid, the 1 : 2 derivative, may be given in doses twice to three times as great as those of phenol without toxic symptoms appearing. The toxic aniline becomes the inert *m*-amido benzoic acid,

$$C_6H_4\begin{cases}NH_2\\COOH,\end{cases}$$

by the introduction of the carboxyl group into the nucleus. The replacement of hydrogen in the methyl group in phenacetin,

$$C_6H_4\begin{cases}OC_2H_5\\NH.COCH_3\end{cases}\ 1:4,$$

with the formation of

$$C_6H_4\begin{cases}OC_2H_5\\NH.CO.CH_2.COOH\end{cases}$$

brings about the loss of its toxic and therapeutic properties.

Allusion may be made here to the **introduction of the acid radical** of either series into physiologically active basic bodies. The radical of acetic acid, or acetyl, $(CH_3CO)'$, of lactic acid, or lactyl,

$$(CH_3.CH\begin{cases}OH\\CO\end{cases})',$$

benzoic acid, or benzoyl, $(C_6H_5.CO)'$, salicylic acid, or salicyl,

$$(C_6H_4\begin{cases}OH\\CO\end{cases})',$$

&c., can readily replace the hydrogen of the amido or imido group through the interaction of the acid itself or the corresponding acid chloride with the base in question (see pp. 36, 43).

The resulting substances are of great importance in the synthetic preparation of drugs; from a chemical standpoint such derivatives are more stable, and less readily oxidized than the bases from which they are obtained. The lactyl substitution products are more soluble than the acetyl, and the salicyl least; and the latter are broken down with such difficulty by the organism that, as a general rule, they do not possess physiological action. The pharmacological reaction of this group of substances is that of the base from which they are obtained.

The action of the benzoyl residue when introduced into the alkaloids is remarkable; thus ecgonine-methyl-ester (see p. 259) has no anaesthetic action, but its benzoyl derivative, i. e. cocaine, possesses most powerful properties.

The toxicity of aconitine stands in intimate relationship to the benzoyl and acetyl groups present in that alkaloid; when these are eliminated the resulting substance has no action. Even splitting off the acetyl residue causes a drop in toxicity, and the loss of the stimulating action, shown by aconitine, on the respiratory centres.

DERIVATIVES OF THE ORGANIC ACIDS.

A. Halogen Substitution Products.

The halogen derivatives of the fatty acids may be obtained, like the parent acids, by the oxidation of chlorinated alcohols or aldehydes,

$$\underset{\text{Chloral.}}{CCl_3.CHO} \rightarrow \underset{\text{Trichloracetic acid.}}{CCl_3.COOH}$$

or by the direct substitution of the hydrogen of the hydrocarbon residue by halogens.

These derivatives have more pronounced acidic properties than the acids from which they are derived, otherwise they show very similar characteristics.

Physiological Action.

The replacement of hydrogen by the halogens, as previously noticed in other cases, causes an increase in narcotic action; thus sodium acetate is quite inert, but sodium monochlor acetate, $CH_2Cl.COONa$, has pronounced narcotic properties; the further replacement of hydrogen, instead of increasing this characteristic, brings about a diminution. Dichloracetic acid has less action than the mono derivative, whereas trichloracetic acid, $CCl_3.COOH$, has very slight, if any, corresponding physiological reaction. In this case the difference in the action may be ascribed to the varying stability of the substances. Monochloracetic is easily decomposed on heating, even at body temperature; trichlor is most stable, and dichloracetic of intermediate stability. It is possible that the narcotic action of the first two acids is due to the liberation of hydrochloric acid in the cerebral cortex, since in animals rendered drowsy by these acids the symptoms are diminished by the injection of sodium carbonate into the vessels. Also, trichloracetic acid does not give rise to hydrochloric acid on decomposition, but to chloroform, and, as already stated, has no narcotic action.

In the other substituted acids the introduction of chlorine sometimes lessens the narcotic action, thus sodium butyrate is more powerful than sodium trichlorbutyrate. Crotonic acid is twice as powerful an hypnotic as the monochlor derivative.

The replacement of hydrogen in acetic acid by bromine and iodine also results in substances with narcotic action, monoiodo acetic acid having less action than the corresponding bromine derivative.

Monobrom- and to a very much less extent monochlor-acetic acid produce muscular rigidity in frogs.

B. The Esters.

The esters of the organic acids resemble very closely those of the mineral acids previously described (p. 93), and are obtained by analogous methods; the most important being the interaction of an acid and alcohol, e. g.

$$CH_3COO\overset{\cdots\cdots}{H} + \overset{\cdots\cdots}{OH}C_2H_5 = H_2O + CH_3COOC_2H_5$$

Ethyl acetate.

As this reaction is reversible (ethyl acetate is decomposed by water with the reformation of alcohol or acid), it is carried out in the presence of hydrochloric or sulphuric acids, or the volatile ester is removed as it is formed.

The esters of the fatty acids are neutral, volatile, pleasant-smelling liquids, generally insoluble in water. They are prepared in large quantities for the artificial production of fruit essences; the acetic ester of amyl-alcohol, $CH_3COO.C_5H_{11}$, in dilute solution is used as pear oil; the octyl ester has the odour of oranges; the isoamyl ester of propionic acid smells like pineapple.

When heated with water, or more rapidly and completely with solutions of the alkalis, they are decomposed into alcohol and acid,

$$CH_3.COOC_2H_5 + KOH = CH_3COOK + C_2H_5OH.$$

Physiological Characteristics.

The loss of the acidic properties of the acids by the replacement of the hydroxyl hydrogen by alkyl groups produces in the esters pharmacological properties closely resembling those of the alcohols.

Ethyl formate, $H.COOC_2H_5$, produces irritation of the throat and

air passages, muscular excitement, stupor but not sleep, and vomiting.

Methyl acetate, $CH_3.COOCH_3$, produces deep stupor; its anaesthetic action is uncertain; there is no muscular excitement.

Ethyl acetate, $CH_3.COOC_2H_5$, acts in a very similar manner to ether, but the action is much slower.

The acetates of the higher fatty radicals have a slower and more prolonged action.

The loss of acidic properties, through the formation of esters, may result in bringing out the main physiological action of the molecule. Thus tyrosin,

$$p\text{-}C_6H_4\begin{matrix}OH\\ CH_2\end{matrix}.CH(NH_2).COOH,$$

is non-toxic, but its ethyl ester,

$$p\text{-}C_6H_4\begin{matrix}OH\\ CH_2\end{matrix}.CH(NH_2).COOC_2H_5,$$

is a powerful poison (dogs).

C. Acid Amides.

The acid amides are derived from the acids by the replacement of hydroxyl by the amido group,

$$CH_3.CO.OH \rightarrow CH_3CO.NH_2.$$

They may be obtained by the distillation of the ammonium salts of the acids,

$$CH_3CO\,O\,NH_2\,H_2 = H_2O + CH_3CONH_2,$$

or by the action of the acid chloride upon ammonia,

$$CH_3COCl + NH_3 = HCl + CH_3CONH_2$$
$$C_6H_5COCl + NH_3 = HCl + C_6H_5CONH_2,$$

or by the action of ammonia upon the esters,

$$CH_5COOC_2H_5 + NH_3 = CH_3CONH_2 + C_2H_5OH$$
$$C_6H_5COOC_2H_5 + NH_3 = C_6H_5CONH_2 + C_2H_5OH.$$

The amides are usually solid crystalline bodies; the lower members of the fatty series are soluble in water, those of the aromatic in boiling water. The introduction of the acidic group into ammonia results in a very considerable drop in basicity. The aliphatic amides unite with acids to form salts, but these are unstable substances.

The amides readily absorb water and pass into the ammonium

salts of the original acids or into ammonia and the acids themselves,

$$CH_3CONH_2 + H_2O = CH_3COONH_4$$

or $$CH_3CONH_2 + KOH = CH_3COOK + NH_3.$$

Physiological Properties.

Formamide and acetamide produce convulsions similar to those set up by picrotoxin; propionamide has less action, and butylamide still less; the action of the last-named only occurs through decomposition and the liberation of ammonia. On the other hand, butylamide has a most powerful narcotic action, and this property decreases in the series till it disappears entirely in the case of formamide. Lactamide and β-oxybutylamide have the same action as propionamide.

The aromatic amides have narcotic properties; this is seen in the case of benzamide, $C_6H_5CONH_2$, although large doses are necessary, and also in the following substances:—

p-methyl benzamide, $C_6H_4\begin{cases}CH_3\\CONH_2\end{cases}$,

the amide of anisic acid,

$$C_6H_4\begin{cases}OC_2H_5\\CONH_2\end{cases}, \qquad 1:2\text{-}C_6H_4\begin{cases}OCH_3\\CONH_2\end{cases},$$

$$1:2\text{-}C_6H_4\begin{cases}OH\\CONH_2\end{cases}, \qquad 1:2\text{-}C_6H_4\begin{cases}OC_2H_5\\CONH_2\end{cases}.$$

Phenylacetamide, $C_6H_5CH_2CONH_2$, is a weaker hypnotic than benzamide. Amidoacetamide, $NH_2.CH_2CONH_2$, has no action, but its benzoyl derivative, the amide of hippuric acid,

$$C_6H_5CO.NH.CH_2CONH_2,$$

has slight narcotic properties.

The amide of cinnamic acid, $C_6H_5CH:CH.CONH_2$, has strong hypnotic properties.

When the hydrogen atoms of the amido group in benzamide are replaced by methyl or ethyl groups, the narcotic action is depressed, and the resulting substance produces symptoms similar to those of ammonia and strychnine. This may be observed in the following series:—

$C_6H_5CONH_2$	$C_6H_5CONH.CH_3$ Methyl benzamide.
$C_6H_5CONH.C_2H_5$ Ethyl benzamide.	$C_6H_5CON(CH_3)_2$ Dimethyl benzamide.

Urea is the diamide of carbonic acid,

$$CO\langle{}^{OH}_{OH} \rightarrow CO\langle{}^{NH_2}_{NH_2}$$

(see p. 216), and it is interesting to note, in connexion with the narcotic properties of benzamide, that benzoyl urea,

$$CO\langle{}^{NHCOC_6H_5}_{NH_2}$$

does not show any similar physiological reaction.

D. The Nitriles.

The nitriles result from the dehydration of the acid amides, e. g.

$$CH_3CONH_2 = CH_3CN,$$

and on the absorption of water pass back into the amides, and then into the acids themselves or their ammonium salts,

$$CH_3CN + H_2O = CH_3CONH_2$$

$$CH_3CONH_2 + H_2O = CH_3COONH_4.$$

They are obtained by the action of dehydrating substances on the acid amides, or by the action of an alcoholic solution of potassium cyanide on an alkyl derivative of the aliphatic series,

$$C_2H_5I + KCN = C_2H_5CN + KI.$$

Another method of preparation consists in the distillation of the potassium alkyl sulphates with potassium cyanide,

$$SO_2\langle{}^{OC_2H_5}_{OK} + KCN = SO_2\langle{}^{OK}_{OK} + C_2H_5CN$$

$$C_6H_5SO_2OK + KCN = K_2SO_3 + C_6H_5CN,$$

The nitriles are liquids usually insoluble in water, possessing an agreeable etherial smell and distilling without decomposition.

Physiological Properties.

The nitrile of formic acid, or prussic acid, HCN, differs from its homologues by its great toxicity. Methyl nitrile, CH_3CN, is, for instance, much less poisonous; but, on the other hand, the isomeric methyl carbylamine, CH_3NC, is extremely toxic, more so it is said than prussic acid, and it seems, therefore, quite likely that prussic acid itself has the constitution HNC, in which nitrogen is quinquevalent.

Bunge found that the nitrile of oxalic acid, i. e. cyanogen,

has one-fourth the toxicity of prussic acid.

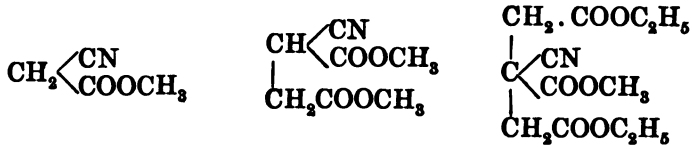
The toxicity of the nitriles of the fatty series increases with the increase of molecular weight; thus Verbrugge found for rabbits:—

Acetonitrile	·13	gm.	per kilo	body weight
Propionitrile	·065	„	„	„
Butyronitrile	·010	„	„	„
Isobutyronitrile	·009	„	„	„
Isovaleronitrile	·045	„	„	„

The introduction of the carboxyl group into acetonitrile lowers the toxicity, thus cyanetic acid = 2·0 gms., the ethyl ester, however = 1·5 gm.

In the aromatic series, benzonitrile is less poisonous, the toxic dose being ·20 gm., for *o*-tolylnitrile it is ·60 gm., and for naphthonitrile 1·0 gm. The introduction of the phenyl residue into acetonitrile raises the toxicity, which, in this case, =·05 gm.

Barthe and Ferre investigated the three substances,



formed by inserting first one $(CH_2COOCH_3)'$ group in cyanacetic methyl ester, and then a second similar group. The first had the most energetic physiological reaction, and was most similar to cyanogen; then came the second, and the third showed no toxic action.

SULPHUR DERIVATIVES.

When oxygen in the alcohols is replaced by sulphur, resulting in the formation of the mercaptans, such as methylmercaptan, CH_3SH, an increase in toxicity is observed, although these derivatives have less physiological action than sulphuretted hydrogen, SH_2. They act mainly on the central nervous system, causing paralysis and convulsions, and finally death from respiratory failure. The mercaptans are characterized by their strong odour, which increases with the molecular weight.

The further replacement of the hydrogen atom by an alkyl group results in sulphides, the analogues of the ethers. Methyl sulphide, $CH_3.S.CH_3$, produces paralysis of central origin; ethyl sulphide is physiologically inactive and has not the powerful odour of the mercaptans; consequently, the physiological reactivity of sulphuretted hydrogen is still further depressed by the replacement of both hydrogen atoms by alkyl groups.

Of the latter derivatives the unsaturated alkyl sulphide,

$$\begin{matrix} C_3H_5 \\ C_3H_5 \end{matrix}\!\!>\!S,$$

has been used for cholera, and in solution in oil for subcutaneous injections in cases of tuberculosis.

In the aldehydes the replacement of oxygen by sulphur is followed by a rise in toxic properties.

Paraldehyde, for example, does not act upon the heart, whereas trithioaldehyde, also possessing hypnotic properties, is a powerful heart poison.

Fatty acids in which sulphur replaces one or two atoms of oxygen are non-toxic.

Carbon bisulphide is a powerful poison, acting mainly on the central nervous system. Workers in caoutchouc factories occasionally develop toxic phenomena—headache, giddiness, deafness, amaurosis, and occasionally paraplegia. Its direct action appears to be narcotic.

The xanthates, e. g.

$$CS\!\!<\!\!\begin{matrix} OC_2H_5 \\ SNa \end{matrix}$$

(substances which are easily decomposed into alcohol and carbon disulphide), have similar physiological action to CS_2; a general narcosis can be produced in man by these bodies. Their alkaline salts are antiseptics.

[*Note.*—Other sulphur compounds will be discussed in connexion with the corresponding oxygen derivatives.]

CHAPTER VI

AROMATIC HYDROXYL DERIVATIVES.—*Main Group of Aromatic Antiseptics.*—Chemical and physiological properties of Phenols, Cresols, Di- and Tri-oxybenzenes. Recent investigations of the antiseptic power of Phenol and its derivatives Creosote, Guaiacol, and their derivatives.

I. MONO-, DI-, AND TRI-OXYBENZENES.

THE substitution of hydrogen in the aromatic nucleus by hydroxyl gives rise to the phenols, a group of substances which correspond to the tertiary alcohols of the fatty series, since they do not yield acid or ketones on oxidation. Like the alcohols they are distinguished as mono-, di-, &c., according to the number of hydrogen atoms replaced by the hydroxyl group.

Methods of Preparation.

1. They may be obtained, as previously indicated (p. 41) by the decomposition of the diazo salts, especially the sulphates, with boiling water,

$$C_6H_5.N:N.HSO_4 + H_2O = C_6H_5OH + N_2 + H_2SO_4$$

2. They also result from the fusion of the sulphonic acids with sodium or potassium hydrate,

$$C_6H_5.SO_2ONa + NaOH = Na_2SO_3 + C_6H_5OH$$

$$C_6H_4\begin{matrix}SO_2ONa\\SO_2ONa\end{matrix} + 2NaOH = 2Na_2SO_3 + C_6H_4\begin{matrix}OH\\OH\end{matrix}$$

General Properties.

The phenols, in contrast to the alcohols, have strongly marked acidic properties, which are enhanced by the entrance of more negative groups into the nucleus. Thus phenol readily gives sodium phenate, C_6H_5ONa, when treated with caustic soda, but is

incapable of decomposing sodium carbonate with the formation of that salt. On the other hand nitro-phenol,

$$C_6H_4\begin{matrix}OH\\NO_2\end{matrix}$$

and picric acid,

$$C_6H_2\begin{matrix}(NO_2)_3\\OH\end{matrix}$$

are sufficiently powerful to liberate carbon dioxide from the carbonate with the formation of the corresponding phenates.

The presence of the hydroxyl group in the benzene nucleus renders more easy the replacement of other hydrogen atoms by chlorine, bromine, or nitro groups.

The hydrogen of the hydroxyl group is readily replaced by alcohol or acid radicals. Thus sodium phenate, treated with methyl or ethyl iodide, gives rise to anisol, $C_6H_5OCH_3$, or phenetol, $C_6H_5OC_2H_5$; these derivatives are very stable and are not decomposed by potash.

The acid esters result from (1) the interaction of phenol or the phenates with the acid chlorides.

$$C_6H_5ONa + CH_3COCl = NaCl + C_6H_5O.(CH_3CO),$$

or (2) digesting the phenols and acids with phosphorus oxychloride or pentachloride.

(3) In the polyhydric phenols all the hydroxyl hydrogen atoms may be replaced by acetyl groups, by heating with acetic anhydride and sodium acetate.

The acid esters resulting from these reactions are readily decomposed into their components by alkalis, thus phenyl acetate,

$$C_6H_5O.OCCH_3 + KOH = C_6H_5OH + CH_3COOK.$$

Nencki, in 1886, was the first to realize the importance of this group of substances for pharmacology, since by their formation both the phenols and acids with which they are combined lose their caustic properties, and the resulting derivatives are slowly broken down only on reaching the intestinal canal, where the physiological action of their components comes into play.

This method of treating phenolic substances is generally termed **Nencki's Salol Principle,** since salol, $C_6H_5O.(OC.C_6H_4.OH)$, was the first of these derivatives introduced.

The acidic nature of the phenols can also be eliminated by the corresponding formation of carbonates, etherial carbonates, or amides. Carbonates are formed by the agency of phosgene,

(i) $C_6H_5ONa + Cl.COCl = C_6H_5O.COCl + NaCl$

and (ii) $C_6H_5O.COCl + H_2O = C_6H_5O.COOH + HCl.$

When ammonia is brought into play at the second phase of the reaction, the amides result,

$$C_6H_5O.COCl + NH_3 = C_6H_5O.CONH_2 + HCl,$$

or such derivatives may be obtained directly by the action of urea chloride on the phenols or their salts,

$$C_6H_5OH + Cl.CONH_2 = HCl + C_6H_5O.CONH_2.$$

The substances of this group are generally solids and are soluble in water.

Chlorformic ester gives rise to the corresponding esters,

$$C_6H_5ONa + Cl.COOC_2H_5 = NaCl + C_6H_5O.COOC_2H_5;$$

bodies of this type are usually liquids, insoluble in water.

The sulphuric esters of phenol have previously been mentioned (p. 102).

Homologous Phenols.

The three cresols *o*, *m*, *p*

$$C_6H_4\begin{matrix}OH\\CH_3\end{matrix}$$

are found in coal-tar and beechwood-tar, thymol,

$$C_6H_3\begin{cases}OH & .\ 1\\CH_3 & .\ 3\\C_3H_7 & .\ 6\end{cases}$$

in oil of thyme. Carvacrol,

$$C_6H_3\begin{cases}OH & .\ 1\\CH_3 & .\ 2\\C_3H_7 & .\ 5\end{cases}$$

in the oil of certain varieties of *satureja*. These substituted phenols cannot be oxidized to their corresponding acids by means of chromic acid, unless the hydrogen of the hydroxyl group is replaced by alkyl or acid radicals.

Polyhydric Phenols.

Several representatives of the dihydric phenols,

$$C_6H_4\begin{matrix}OH\\OH,\end{matrix}$$

are found in plants or may be obtained as decomposition products of plant substances.

Pyrocatechol,

$$C_6H_4\begin{matrix}OH\\OH\end{matrix}\ 1:2,$$

may be obtained by the distillation of catechin, and by fusing many resins with potash. Its monomethyl ether, pinacol,

$$C_6H_4\begin{matrix}OH\\OCH_3,\end{matrix}$$

occurs in creosote from beechwood-tar, a homologue, eugenol,

$$C_6H_3\begin{cases}C_3H_5 & 1\\OH & 4\\OCH_3 & 3\end{cases}$$

occurs in oil from *Eugenia caryophyllata*, &c.

Resorcinol, $C_6H_4(OH)_2$ 1 : 3, is the most important member of the group, and may be obtained from asafoetida, galbanum, and other resins by heating them with potash. Its methyl homologue, orcin,

$$C_6H_3\begin{cases}CH_3 & 1\\OH & 3\\OH & 5\end{cases}$$

is found in many lichens.

Hydroquinone, $C_6H_5(OH)_2$ 1 : 4, is so called on account of the ease with which it may be obtained by the reduction of quinone.

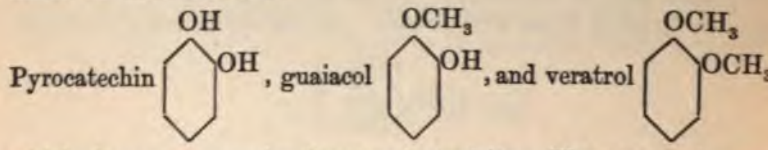
Pyrogallic acid, $C_6H_3(OH)_3$ 1 : 2 : 3, is the best known member of the trihydric phenols, its dimethyl ether is found in beechwood creosote. It is less stable than the dioxy and still less than monoxybenzenes, it readily reduces salts of silver, mercury, and gold, with the formation of the metals and the complete breakdown of the ring nucleus into acetic and oxalic acids.

Physiological Properties of the Phenols.

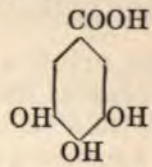
The entrance of the hydroxyl group into benzene, with the formation of phenol, causes a great increase in antiseptic and toxic properties. Phenol and its homologues in large doses produce convulsions of spinal origin, an action which is not so marked in the higher members of the series. The introduction of long aliphatic side-chains, or of several alkyl groups hinders this action. The phenols also act on nerve endings. Large doses paralyse motor nerve endings, while small doses have a marked local anaesthetic action. The old-fashioned remedy for an aching tooth is to fill the cavity with a clove, which owes its anaesthetic properties to eugenol.

Phenol itself or the oil of cloves is frequently used for the same purpose. The antipyretic action of the benzene ring, which is not lost in the phenol series, cannot be utilized for obvious reasons.

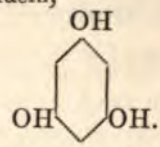
The action on the spinal cord decreases with the number of hydroxyls, but in other respects the toxicity is increased. Thus phenol and the dioxybenzenes produce spasms in frogs, whereas trioxybenzene (1 : 2 : 3) only produces shivering; on the other hand, the animal becomes more comatose and atoxic than with resorcin. Binet holds that the toxic symptoms (collapse and convulsions) of the phenols are traceable to the benzene nucleus, but are modified by the introduction of OH or acyl groups. The antagonistic action of these is seen in



which show a progressive decrease in toxicity. The carboxyl group also modifies the toxicity; gallic acid,



produces no shivering, and is a much less powerful blood poison than pyrogallol. The lower phenols are protoplasmic poisons, causing coagulation, but this property is lost in the higher members of the series, e.g. phloroglucin,



The toxic properties of the phenols are depressed by the replacement of hydrogen atoms in the nucleus by alkyl groups, whereas the antiseptic characteristics are increased. This alteration, however, is more marked with 1 : 3-cresol than with the others; recent investigations have shown that the toxicity of 1 : 2-cresol lies very near that of phenol, whereas 1 : 4-cresol is greater. As regards antiseptic properties the 1 : 3 derivative is more powerful than the 1 : 4, and ortho cresol is the weakest of the three.

Koch and Lubbert have drawn attention to the great value of thymol,

$$C_6H_3\begin{cases}OH & 1\\ CH_3 & 3\\ C_3H_7 & 6\end{cases}$$

as an antiseptic.

The homologous phenols, however, are much less soluble in water than phenol itself, and various methods have been tried by which to modify this factor. The majority of these have been based on the use of different solvents, the solution, for instance, of these derivatives in various fats, or in solutions of different salts, such as caustic soda, soaps, or calcium hydrate.

Metakalin, for instance, is a solid compound of pure *m*-cresol and potassium cresotinate,

$$C_6H_3\begin{cases}CH_3\\ OH\\ COOK,\end{cases}$$

in a sodium soap, and it contains the least toxic but most powerfully antiseptic of the three cresols.

Lysol is oil of tar mixed with linseed or a fatty oil, and completely saponified with potash in the presence of alcohol. It is not so irritating or so toxic as carbolic, and may vary in antiseptic strength owing to varying proportions of the different cresols.

Creolin is an emulsion of cresols in resin soap, and is destroyed by mineral acids, caustic alkalis, and sodium chloride. It contains varying amounts of the different cresols.

Cyllin, an improved preparation of creolin, has a bactericidal power sixteen times that of pure phenol (Rideal) when tested with B. Typhosus—'medicinal' cyllin was used. Klein finds it thirty times as strong when tested with B. pestis.

Jonesen[1] experimented with dogs in nitrogenous equilibrium, observing the effects of cresols on their output of nitrogen, ammonia, and indigo. The cresol was entirely eliminated by the urine, none was ever found in the faeces. During the periods in which cresol was given the ammonia decreased, owing to the conjugation of the H_2SO_4 with cresol. The effect on indigo varied with the different isomers, the greatest augmentation occurred with *ortho-*, and the least with *meta*-cresol, the *para* derivative being intermediate. The cresols are also to a smaller extent conjugated with glycuronic acid, the amount

[1] *Biochem. Zeitschr.*, vol. i, fasc. 5 and 6, pp. 399–407, 1907.

being greater the more toxic the cresol. The total amount recoverable from the urine also varied directly with the toxicity. With *meta*-cresol it was 46-5 per cent., with *ortho*-cresol 30-35 per cent., and with *para*-cresol it fell to 25 per cent. of the amount ingested. These phenomena, as also the toxicity, may of course be merely the results of variations in the rapidity of absorption.

Bechhold and Ehrlich[1] have recently investigated various phenol derivatives, and have shown—1. that the entrance of chlorine or bromine into the nucleus of phenol causes an increase in antiseptic power. In the following comparisons an amount of phenol equal to 1,000 gm. molecules was taken, and against it were compared the quantities of various substances, also in gm. molecules, necessary to prevent the growth of certain bacteria in a given fluid.

Phenol		1000	Diphtheria bacillus	
Trichlor	„	>40	„	„
Tribrom	„	>22	„	„
Tetrachlor	„	16	„	„
Pentachlor	„	7	„	„
Pentabrom	„	2	„	„

In the last case, for instance, one gm. molecule of pentabrom phenol has the same action in preventing the growth of diphtheria bacillus as 500 gm. molecules of phenol.

2. The entrance of alkyl groups into the nucleus of phenol, as previously mentioned, increases its antiseptic value, and a similar increase was noticed in the case of the halogen derivatives; thus

Phenol	=	1000	Diphtheria bacillus	
Tetrachlor „	=	16	„	„
$C_6Br_4\langle^{CH_3}_{OH}$ Tetrabrom-*o*-cresol	=	9	„	„
„ „ „ *m*- „	=	2-2	„	„
„ „ „ *p*- „	=	1-1	„	„
Tetrabrom phenol	=	>22	„	„
$C_6HBr_2\langle^{(CH_3)_2}_{OH}$ Dibrom-*p*-xylenol	=	3-9	„	„
$C_6Br_3\langle^{(CH_3)_2}_{OH}$ Tribrom-*m*-xylenol	=	<1-3	„	„
$C_6(CH_3)_3\langle^{Br_2}_{OH}$ Dibrompseudo cuminol	=	6-5	„	„

[1] —ppe-Seyler's *Zeit. für. Phys. Chem.*, 47, 173, 1906.

That is, tribrom-*m*-xylenol is twenty times as active as tribrom-phenol. Tetrabrom-*o*-cresol is about sixteen times as active as tetrachlor-phenol. This brominated cresol is but very slightly toxic; a one per cent. solution kills diphtheria bacillus in less than two minutes, whereas a corresponding one per cent. phenol solution requires more than ten. Further, the same strength solution kills bacillus coli in less than five minutes, whereas phenol requires sixty.

3. The combination of two phenol nuclei, as, for example, *p*-dihydroxy-diphenyl,

$$\begin{array}{l} C_6H_4.OH \\ | \\ C_6H_4.OH, \end{array}$$

or the derivatives of diphenyl methane, such as those given in the following table, as well as their chlorinated derivatives, are more powerful than phenol.

Phenol	= 1000	Diphtheria	bacillus
p-dioxy-diphenyl, $OH.C_6H_4.C_6H_4.OH$	= 47	,,	,,
Tetrachlor phenol	= 16	,,	,,
Tetrachlor-*o*-diphenyl, $OH.C_6H_2Cl_2.C_6H_2Cl_2.OH$	= ·7	,,	,,
Tetrabrom-*o*-diphenyl, $OH.C_6H_2Br_2.C_6H_2Br_2OH$	= ·4	,,	,,
Tetrabrom-*p*-dioxy-diphenyl methane, $CH_2(C_6H_2Br_2OH)_2$	= 1·8	,,	,,
Hexabrom-*p*-dioxy-diphenyl methane, $CH_2(C_6HBr_3OH)_2$	= <1·4	,,	,,
Hexabrom-*p*-dioxy-diphenyl carbinol, $CH.OH.(C_6HBr_3OH)_2$	= ·6	,,	,,

4. The combination of two phenol groups by means of CO or SO_2 decreases the antiseptic power.

Phenol	= 1000	Diphtheria	bacillus
Tetrabrom-dioxy-diphenyl-methane	= 1·8	,,	,,
Tetrabrom-dioxy-benzophenone, $OH.C_6H_2Br_2.CO.C_6H_2Br_2OH$	= >177	,,	,,
Tetrabrom-dioxy-diphenyl-sulphone, $OH.C_6H_2Br_2.SO_2.C_6H_2Br_2OH$	= <34	,,	,,

5. The entrance of the acid grouping (COOH) depresses the antiseptic power of the phenols.

	Phenol = 1000	Diphtheria bacillus	
Tetrachlor phenol, $C_6H.Cl_4.OH$	= 16	„	„
Tetrachlor-*m*-oxybenzoic acid, $C_6Cl_4\langle^{OH}_{COOH}$	= 683	„	„
Trichlor phenol, $C_6H_2Cl_3.OH$	= >40	„	„
Trichlor-phenoxy-acetic acid, $C_6HCl_3\langle^{OH}_{CH_2COOH}$	= >740	„	„
Tribrom phenol	= 22	„	„
Tribrom-phenoxy-acetic acid, $C_6HBr_3\langle^{OH}_{CH_2COOH}$	= 490	„	„

As regards the relative toxicity of the halogen derivatives of phenol, it is found that the entrance of a bromine atom reduces the convulsant action, so characteristic of phenol itself, and also lowers the toxicity, but the further introduction causes a rise in this characteristic, and tribrom or trichlor phenol are about equal to phenol itself, whereas tetra and penta halogen derivatives are more powerful; the latter in fact may be regarded as very toxic substances.

All the solutions were made up with the same amount of alkali, viz. 100 c.c. solution contained 6·5 c.c. of normal caustic soda. It was observed that the toxicity of phenol and *o*-cresol was depressed in such solutions.

	Toxic dose for white mice 1000 gms. in weight		
	in alkali solution of 6·5 c.c. NaOH in 100 c.c. solution.	without alkali	
	gms.	gms.	
Phenol	·25	·20	immediate spasms.
Monobrom-phenol	·35	—	„ „
Trichlor „	·24	—	spasms after a few minutes.
Tribrom „	·28	—	spasms after a few minutes.
Tetrachlor „	·12	—	slight spasms shortly before death.
Pentachlor „	·056	—	no spasms.
o-cresol	·41	·32	immediate spasms.
Tetrabrom-*o*-cresol	·44		no spasms.

The following substances were also investigated :—

(a) Tetrabrom-hydroquinone-phthalein.

B. Diphtheriae. Antiseptic 1 in 80,000 (compared with 1 in 200,000 $HgCl_2$). Bactericidal 1% solution, more than 2 less than 6 minutes; ·5% solution, 10 minutes (compared with 1‰ $HgCl_2$ less than 1 minute).

B. Typhosus. 1 in 400, no antiseptic action.

B. Pyocyaneus. No bactericidal action. 3% in 60 minutes (compared with 5‰ $HgCl_2$ in less than 15 minutes).

Animal Experiments.

Guinea-pigs, weight 250–370 gms. 1% solution: 3 c.c. subcutaneously and 5·7 c.c. by oesophageal tube—no action; 3 c.c. intraperitoneally caused death (peritonitis).

(b) Tetrabrom-hydroquinone-phthalein-oxime.

B. Diphtheriae. Antiseptic 1 in 80,000; bactericidal 1‰ in more than 15 minutes.

B. Typhosus. No antiseptic or bactericidal action in 1 in 200.

M. Gonorrhoeae. Antiseptic and bactericidal in 1 in 1,600.

Animal Experiments.

Guinea-pigs, 250–510 gms. weight. 1% solutions: subcutaneously 3 c.c. were painful; no other effect. 1 c.c. intraperitoneally, no action. Repeated doses 16 c.c. by oesophageal tube produced traces of albumin in urine, but no other action.

(c) Hexabrom-dioxyphenyl-carbinol.

B. Diphtheriae. Antiseptic and bactericidal in 1 in 320,000 solution.

B. Pseudodiphtheriae. Antiseptic 1 in 128,000.

Streptococcus Pyog. Antiseptic 1 in 5,000.

B. Coli. Antiseptic 1 in 80.

B. Pyocyaneus. Antiseptic 1 in 400.

B. Coli. Bactericidal 3% solution in over 60 minutes.

Staphylococci. Bactericidal 1% solution from 30 to 60 minutes.

B. Pyocyaneus. 5% solution in NaOH from 15 to 30 minutes. Meat could not be sterilized with 1 in 200, nor serum with 1 in 100, nor milk with 1 in 1,000.

Animal Experiments.

White mouse, weight 15 gms. 1 % solution ·8 c.c. intraperitoneally killed in 30 minutes. *Rabbit*, 2,100 gms., 45 c.c. of 1·5 % solution intravenously was fatal. *Guinea-pigs* weighing 300 gms. showed only transient paralysis of hind limbs when 1 c.c. of a 3 % solution was injected intracardially. Others weighing 500 to 620 gms. took 25 c.c. of a 1 % solution *per os*. Most of the bromine derivative was excreted in the faeces in 7 days.

Man. 10 c.c. of 1 % solution *per os* produced no ill effects. The taste is unpleasant and burning.

Rabbits, guinea-pigs, and mice infected with various organisms were given this solution in various ways (intravenously, &c.) but without any effect.

(d) Hexabrom-dioxyphenyl-methoxy-methane.

B. Diphtheriae. Antiseptic 1 in 200,000 to 1 in 640,000; bactericidal 1 in 320,000.

B. Pyocyaneus. Antiseptic 1 in 400.

Animal Experiments.

White mice, about 15 gms. weight. 1 % solution, ·8 c.c. fatal subcutaneously. Local necrosis. Sublethal doses had no effect on animals infected with trypanosomiasis.

(e) Tetrachlor-ortho-diphenol and tetrabrom-ortho-diphenol.

B. Diphtheriae. Antiseptic 1 in 200,000 to 1 in 640,000; bactericidal 1 % in less than 2 minutes.

B. Coli. Bactericidal 1 %, 5 to 30 minutes.

Animal Experiments.

The bromide only was used. ·3 gms. in 10 c.c. was fatal for guinea-pigs subcutaneously. ·1 c.c. of 1 % solution intraperitoneally and ·25 c.c. subcutaneously was fatal for white mice. No effect was produced on infected animals by injections with sublethal doses.

(f) Tetrabrom-ortho-cresol.

B. Diphtheriae. Antiseptic 1 in 200,000–160,000; bactericidal 1 in 320,000.

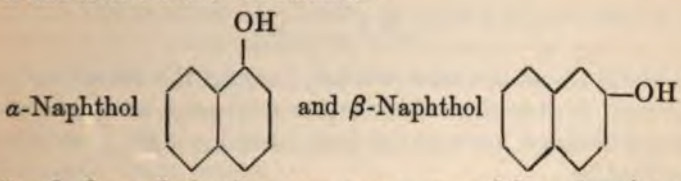
B. Coli. Bactericidal 1 % solution in less than 5 minutes.

Animal Experiments.

Guinea-pigs treated with 1 gm. in 16·5 c.c. water with addition of caustic soda gradually lost weight and died after 28 days. Cause not obvious. For *white mice* the fatal dose subcutaneously was ·44 gm. per 1,000 gm. body-weight. Sublethal doses had no effect on mice infected with streptococci.

The **general conclusion** from these experiments was that, though some of these bodies were powerful disinfectants, none of them were more damaging to bacteria than to the animal body when used as internal disinfectants. Similar conclusions were arrived at by one of the present writers[1] with regard to perchloride of mercury, oxycyanide of mercury, formic aldehyde, chinosol, protargol, and sodium taurocholate, and by Dr. W. V. Shaw[2] for formalin, guaiacol and chinosol.

The introduction of hydroxyl into the nucleus of naphthalene gives rise to two isomeric substances



Both of these derivatives are more powerful antiseptics than phenol; the α derivative is more toxic than the other, and in consequence is not employed in medicine. Owing to its slight solubility, β-naphthol is only used in dermatology; its sodium salt, which is much more soluble in water, goes by the name of **Mikrocidine**. In order to increase the solubility, the β-naphthol sulphonic acid was investigated, but it was found that the introduction of the acid group had considerably lowered the antiseptic action. These derivatives go by the name of **Asaprol** or **Abrastol**, and are the potassium or calcium salts of β-naphthol-α-sulphonic acid. To lessen the caustic action and diminish the toxicity, β-naphthol was converted into acid esters according to the salol principle. Thus **Betol** is the salicylic ester, $C_{10}H_7O.(OC.C_6H_4OH)$, and benzonaphthol, introduced by Yvon and Berliez in 1891, the benzoic acid ester, which is formed by the action of benzoyl chloride on β-naphthol,

$$C_{10}H_7.OH + C_6H_5COCl = HCl + C_{10}H_7O.(COC_6H_5).$$

[1] *Guy's Hospital Reports*, vol. lviii.
[2] *Journal of Hygiene*, April, 1903.

This derivative, like the previous one, is decomposed into its constituents in the small intestine by the pancreatic juice and bacteria.

Epicarin, introduced in 1899, β-oxynaphthol-*o*-oxy-*m*-toluic acid,

$$HO.C_{10}H_6\left[-CH_2-C_6H_3\begin{matrix}COOH\\OH\end{matrix}\right]$$

is obtained by the action of chlormethylsalicylic acid on β-naphthol dissolved in acetic acid,

$$C_6H_3\begin{matrix}COOH\\OH\\CH_2Cl\end{matrix} + C_{10}H_7OH = C_6H_3\begin{matrix}COOH\\OH\\CH_2-C_{10}H_6.OH\end{matrix} + HCl.$$

It has powerful acid properties, and forms salts soluble in water. It is a powerful and non-irritating antiseptic, and is mainly excreted unchanged. It has been used as an antiparasitic for the skin.

β-naphthylamine sulphonic acid,

$$C_{10}H_6\begin{matrix}OH\\SO_2OH,\end{matrix}$$

very readily combines with nitrites, forming the innocuous diazo compound. It has thus been employed in cases of poisoning by nitrites, and also to prevent the urine becoming alkaline in diseases of the bladder.

The action of the halogen derivatives of naphthol has not been investigated.

POLYHYDRIC PHENOLS.

I. A. Dioxybenzenes.

According to Fränkel, the toxicity and the antiseptic action increases with the number of hydrogen atoms in the benzene nucleus replaced by hydroxyl groups. On the other hand, Schmiedeberg states that one of the dioxybenzenes, i. e. resorcin,

$$C_6H_4\begin{matrix}OH\\OH\end{matrix}\ 1:3,$$

is less toxic, and has less antiseptic power than phenol. The trioxy derivative, pyrogallol, $C_6H_3(OH)_3$, however, is certainly more poisonous than resorcin. Of the three isomeric dioxybenzenes, the 1:2 derivative, pyrocatechin, is the most toxic, then the 1:4 hydroquinone, whilst resorcin, the 1:3 derivative, is the least poisonous, and consequently the only isomer employed in medicine. It is formed by fusing any of the disulphonic acids with caustic soda,

which means that an intramolecular change takes place with the 1 :4 and 1 :2-sulphonates, and that 1 :3-dioxybenzene is the most stable of the three isomers at the temperatures requisite for such reactions.

The monoacetyl derivative

$$1:3\ C_6H_4\begin{cases}OH\\O.COCH_3\end{cases}$$

goes by the name of **Euresol.**

B. Etherial Derivatives of Dioxybenzenes.

Creosote from beechwood-tar consists chiefly of a mixture of phenol, cresols, guaiacol,

$$1:2\ C_6H_4\begin{cases}OCH_3\\OH\end{cases}$$

and its homologues, creosol,

$$C_6H_3(CH_3)\begin{cases}OCH_3\\OH\end{cases}$$

Owing to the presence of phenols, the action of creosote is very similar to that of phenol itself. It has antiseptic properties, but is toxic and has caustic action. The latter depends on the presence of the free hydroxyl grouping, and many derivatives have been introduced, based on the salol principle, in order to overcome this objectionable characteristic.

The esters which have been prepared for this purpose all break down into their components in the intestine.

Creosote carbonate, for instance, like creosote itself—a mixture of several substances—is obtained by the action of carbonyl chloride on an alkaline solution of creosote. The formation of the ester of carbonic acid by this means produces a very great drop in toxicity and the loss of the caustic action of the original mixture.

Other esters of creosote have been prepared and introduced into medicine, but these have been all replaced by what is supposed to be the most powerful physiological agent present in the mixture, viz. guaiacol, or its derivatives. It is probable, though, that the methyl ester of homobrenzcatechin,

$$C_6H_3\begin{cases}CH_3\\OCH_3\\OH\end{cases}$$

which is present in creosote, may be an important constituent, since, judging from what has been previously stated, its toxicity should be less, but its antiseptic value greater, than that of guaiacol, which has no methyl group substituted in the nucleus. This homologue is

difficult to isolate from the mixture, and has not yet been introduced into pharmacology.

Guaiacol is obtained from anisol by nitration, and reduction of resulting 1:2-nitro anisol to the amido derivative; this is then diazotized and boiled with water.

$$C_6H_4.OCH_3 \rightarrow C_6H_4\begin{matrix}NO_2\\OCH_3\end{matrix} \rightarrow C_6H_4\begin{matrix}NH_2\\OCH_3\end{matrix}$$

$$\rightarrow C_6H_4\begin{matrix}N:N.OH\\OCH_3\end{matrix} \rightarrow 1:2\ C_6H_4\begin{matrix}OH\\OCH_3\end{matrix}$$

It is a toxic substance, and irritates the gastric mucosa. Its subcutaneous use is dangerous, owing to the collapse and cardiac depression it may produce. In toxic doses it produces excitation, followed by paralysis of the central nervous system, the former symptoms being less marked in the higher animals. It is less toxic and more powerfully antiseptic than phenol.

Inorganic Acid Esters of Guaiacol.

A. 1. Guaiacol carbonate or **Duotal,**

$$CO\begin{matrix}OC_6H_4.OCH_3\\O.C_6H_4.OCH_3\end{matrix}$$

results from the interaction of carbonyl chloride and the sodium salt of guaiacol.

$$2C_6H_4\begin{matrix}OCH_3\\ONa\end{matrix} + COCl_2 = 2NaCl + CO(OC_6H_4.OCH_3)_2$$

In this reaction guaiacol may be replaced by a large number of hydroxyl derivatives, such, for instance, as menthol, eugenol, carvacrol, &c.

Creosotal (creosote carbonate) and **Duotal** are both insoluble, and therefore tasteless. The former is a yellow almost odourless liquid miscible with alcohol and oils, and the latter a white crystalline powder slightly soluble in oil and glycerin.

2. Mixed carbonates of aromatic and aliphatic radicals may be obtained by the action of chloroformic esters on sodium guaiacol or other allied substances, such as eugenol, creosol, and carvacrol,

$$C_6H_4\begin{matrix}OCH_3\\ONa\end{matrix} + Cl.COOC_2H_5 = NaCl + CO\begin{matrix}OC_2H_5\\O.C_6H_5.OCH_3\end{matrix}$$

Ethyl-guaiacol carbonate.

or generally

$$X.ONa + Cl.COOR = NaCl + CO\begin{matrix}OR\\OX\end{matrix}$$

The resulting derivatives, in distinction to the carbonate, are liquids, and on this ground are suitable for injection, but have little practical importance.

3. Carbamic esters of guaiacol and allied substances can be obtained by the interaction of urea chloride and the phenol or its sodium salt.

$$C_6H_4\begin{matrix}OCH_3\\ONa\end{matrix} + Cl.CONH_2 = NaCl + CO\begin{matrix}NH_2\\O.C_6H_4.OCH_3\end{matrix}$$

Instead of guaiacol, the following hydroxyl derivatives have been employed:—Menthol, carvacrol, eugenol, thymol, geraniol, &c.

B. Phosphate of guaiacol or **Phosphatol**, $PO(OC_6H_4.OCH_3)_3$, was intended to combine the action of phosphorus with that of the cresol in cases of tuberculosis.

C. Phosphite of guaiacol (**Guaiacophosphal**) is obtained by the action of phosphorus trichloride on the sodium salt,

$$PCl_3 + 3C_6H_4\begin{matrix}OCH_3\\ONa\end{matrix} = 3NaCl + P(O.C_6H_4.OCH_3)_3.$$

It is a crystalline powder, and, in distinction to the phosphate and carbonate, is soluble in fatty oils. Under the name **Phosphotal** is sold a mixture of the phosphorous ethers of the creosote phenols (neutral phosphites) containing 90 per cent. creosote and 9 per cent. P_2O_3. It is not caustic and is much less toxic than creosote.

D. Mixed sulphuric esters of phenols and aliphatic radicals have been obtained by the action of ethylchlorsulphuric acid upon alkaline solutions of guaiacol.

$$SO_2\begin{matrix}OC_2H_5\\Cl\end{matrix} + C_6H_4\begin{matrix}OCH_3\\ONa\end{matrix} = NaCl + SO_2\begin{matrix}OC_2H_5\\O.C_6H_4.OCH_3\end{matrix}$$

The various phenolic substances previously mentioned may be used in place of guaiacol, and the ethyl group can be replaced by methyl, butyl, &c.

Organic Acid Esters of Guaiacol.

Various aliphatic acid esters of guaiacol and similar phenols, or of the mixture creosote, have been prepared. They are formed by heating a mixture of the acid, phenol, and a dehydrating agent, such as phosphorus trichloride, to a temperature of 135°. Thus in the case of oleic acid,

$$CH_3.(CH_2)_7.CH:CH(CH_2)_6.CH_2CO\boxed{OH} + C_6H_4\begin{matrix}OCH_3\\\boxed{OH}\end{matrix}$$

$$= H_2O + C_6H_4\begin{matrix}OCH_3\\O.CO(C_{17}H_{33})\end{matrix} \text{ (Guaiacol oleate),}$$

this ester is liquid and insoluble in water.

The valerianic ester or **Geosote**,

$$1:2\ C_6H_4\begin{cases}OCH_3\\O.COC_4H_9\end{cases}$$

is also a liquid insoluble in water, only slightly soluble in dilute acids and alkalies, and soluble in large quantities of alcohol, ether, chloroform, &c. It has an oily character and a penetrating aromatic odour. **Eosote** is a similar preparation, said to be less pure.

Further description of this group is unnecessary, and it is hardly likely that derivatives of pharmacological value greater than the carbonate can be found in this class.

In a similar manner, aromatic acid esters have been prepared and investigated. Thus the benzoic acid ester of guaiacol or **Benzosol**,

$$C_6H_4\begin{cases}OCH_3\\O.OC.C_6H_5,\end{cases}$$

has been introduced, but this substance is decomposed with rather more difficulty than the carbonate, and its product, benzoic acid, is of little pharmacological value, except possibly as an expectorant and urinary disinfectant.

The salicylic acid ester or **Guaiacolsalol**,

$$C_6H_4\begin{cases}OCH_3\\O.OC.C_6H_4OH,\end{cases}$$

like the previous derivative, is a solid with low melting-point, which breaks down in the small intestine into guaiacol and the antiseptic salicylic acid, but again this decomposition does not take place at all readily, and in order to decrease the stability of these aromatic esters an amido group has been introduced into the 1 : 4 position in the benzoyl radical—*p*-acetamido-benzoyl-guaiacol,

$$C_6H_4\begin{cases}OCH_3\\O.C_6H_4.NH(COCH_3).\end{cases}$$

This substance may be obtained by the action of 1 : 4-nitrobenzoyl chloride on sodium guaiacol.

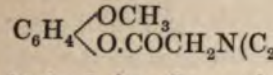
$$C_6H_4\begin{cases}NO_2\\COCl\end{cases}+C_6H_4\begin{cases}O.CH_3\\ONa\end{cases}=NaCl+C_6H_4\begin{cases}OCH_3\\O.COC_6H_4NO_2\end{cases}$$

The resulting substance is then reduced, and the acetyl group introduced in the ordinary way.

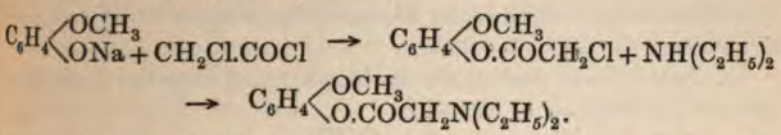
Although this derivative is decomposed with greater ease than the benzoic acid ester, it is improbable that its value can be greater than others previously mentioned.

Attempts to increase Solubility of Guaiacol.

A. Einhorn and Hütz have introduced the hydrochloric acid salt of diethyl-glycocoll-guaiacol, or **Guaiasanol,**



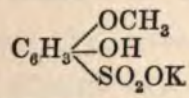
This may be obtained by the action of diethylamine on the chloracetyl derivative of guaiacol,



This substance is soluble in water, precipitated as an oily base by carbonates, and is broken down in the intestine in the usual way. Its antiseptic action is equal to that of boracic acid, it is slightly anaesthetic and very slightly toxic. Three grams subcutaneously in rabbits produced no symptoms.

B. The simplest method of increasing solubility is to form the sulphonic acids, whose sodium or potassium salts are soluble in water. This has been carried out with guaiacol, although the resulting compound is no exception to the general rule that such derivatives have less physiological action than the parent substance.

1 : 2-guaiacolsulphonate of potash, or **Thiocol,**



was introduced by C. Schwarz in 1898, and may be obtained by the sulphonation of guaiacol at a temperature below 80° C. The introduction of the sulphonic group results in a complete loss of the characteristic taste and smell of guaiacol, and a lowering of antiseptic power. As might be expected from the presence of the acid grouping, it passes unchanged through the body.

The 1 : 4-sulphonic acid of guaiacol results when the sulphonation is carried out at higher temperatures, but this derivative and its salts have no pharmacological value owing to their objectionable action on the stomach.

The process of sulphonation can clearly be carried out with a large number of phenol substances, or with such mixtures as creosote, but in all cases the resulting substances will have less antiseptic power.

Sulphosote and **Sirolin** are preparations of thiocol combined with flavouring agents.

C. It has been found that the glycerin ester of guaiacol, or **Guaiamar**,

$$C_6H_4\begin{cases}OCH_3\\O.C_3H_5O_2,\end{cases}$$

is soluble in water; it may be obtained by the action of monochlorhydrin on sodium guaiacol, or by treating the phenol and glycerin with a dehydrating substance. It is decomposed in the body like the other esters, but its bitter aromatic taste appears to be against its use as a guaiacol substitute.

D. The introduction of the carboxyl group into the nucleus of guaiacol, giving rise to the acid

$$C_6H_3\begin{cases}OCH_3\\OH\\COOH\end{cases}$$

results in a substance with less antiseptic power and no great advantage over the phenol itself owing to its slight solubility.

E. By the action of monochloracetic acid on 1 : 2-dioxybenzene in presence of an alkali, there results brenzcatechin-monoacetic acid,

$$C_6H_4\begin{cases}ONa\\OH\end{cases} + ClCH_2COOH = C_6H_4\begin{cases}O.CH_2COOH\\OH\end{cases}$$

This substance goes by the name of **Guaiacetin**; it is soluble in water and almost tasteless. It is similar to guaiacol in the toxic symptoms it produces.

GENERAL REMARKS ON CREOSOTE DERIVATIVES.

The only active constituent of creosote which has been at all widely employed is guaiacol, $C_6H_4.OCH_3.OH$. Other bodies have, however, been isolated, such as creosol, the monomethyl ether of homopyrocatechin,

$$C_6H_3\begin{cases}CH_3\\OCH_3\\OH\end{cases}$$

which has been previously mentioned.

Veratrol, the dimethyl ether $C_6H_4(OCH_3)_2$, though less toxic is more irritating to the gastric mucosa than guaiacol. The corresponding monoethyl ether

$$C_6H_4\begin{cases}OC_2H_5\\OH\end{cases}$$

is much more expensive and appears to have no therapeutic advantages.

Of the numerous guaiacol derivatives none fulfil all the conditions at which the pharmacologists aimed. The desideratum is a guaiacol which shall be easily soluble in water, tasteless, and non-irritating. The solubility cannot be combined with absence of taste. The only substance which appears to combine these characters is thiocol, the etherial sulphate of guaiacol and potassium. This, however, is the form in which guaiacol is ordinarily excreted, hence it is not remarkable that it passes unchanged through the body. Thus it cannot liberate guaiacol or exert any antiseptic action. It does not appear that any guaiacol derivative which is not broken up in the body with the liberation of guaiacol can exert any antiseptic action. Knapp and Suter investigated several compounds, taking as an index the amount of sulphonic acid esters excreted. Guaiacol cinnamic acid ester liberated 84·94 per cent., guaiacol carbonate 50 per cent.; guaiacol glyceric ether, which is antiseptic in itself, is mainly absorbed as such, very little appearing in the urine as the sulphur compound. The synthesis of other bodies with guaiacol may or may not be an advantage; probably it is the guaiacol itself which is the important factor in all these cases. Thus in the cinnamic acid compound it is more than doubtful whether this combination has any real advantage beyond that which it obtains from the facility with which guaiacol is liberated in the body.

II. Trioxybenzenes.

Pyrogallol, $C_6H_3(OH)_3$ 1:2:3, is the only trioxy derivative employed in medicine, it has antiseptic properties and is mainly employed as an application for psoriasis. It is a very toxic body, causing the usual symptoms of poisoning by phenols if it is absorbed to any extent. It is partly excreted as a sulphonic acid ester in the urine.

Eugallol, monacetyl pyrogallol, $C_6H_3(OH)_2O.COCH_3$, is very similar in its action to pyrogallol, but the toxicity is said to be decreased.

Lenigallol is triacetyl pyrogallol, $C_6H_3(O.COCH_3)_3$; it is non-toxic and non-irritant, owing to the replacement of the three hydroxyl hydrogen atoms by acetyl groups. Its action on the skin is very much less powerful, owing to the slow formation of pyrogallol; it is thus unsuited to cases where a rapid reducing agent is required.

Another derivative of pyrogallol is **Galla-acetophenone**, or methyl-keto-trioxybenzene, $CH_3 . CO.C_6H_2(OH)_3$; it is obtained by heating pyrogallic acid, acetic acid, and a dehydrating agent such as zinc chloride. It has powerful antiseptic properties, and is less toxic than pyrogallol. It does not stain linen, but is not such an active local application for psoriasis.

CHAPTER VII

AROMATIC HYDROXYL DERIVATIVES (CONTINUED). *The Hydroxy Acids.*—Classification of Salicylic acid derivatives. Nencki's Salol Principle. Tannic and Gallic Acids.

HYDROXYBENZOIC ACIDS.

IT has been previously remarked that the pharmacological reaction of benzene is very considerably diminished by the introduction of the carboxyl group, and the resulting benzoic acid, C_6H_5COOH, may be given in large doses without much physiological result. On the other hand, the phenyl substitution products of the aliphatic acids, such as phenyl acetic, $C_6H_5.CH_2COOH$, phenyl propionic, $C_6H_5CH_2.CH_2.COOH$, and phenyl butyric acid,

$$C_6H_5CH_2.CH_2.CH_2.COOH,$$

show antiseptic power stronger than phenol and increasing with increase of molecular magnitude.

The unsaturated cinnamic acid, $C_7H_5CH:CH.COOH$, in the form of its sodium salt, the so-called **Hetol,** was introduced by Landerer in 1892. It may be obtained by the condensation of benzaldehyde and acetic acid (Perkin's synthesis),

$$C_6H_5CHO + H_2CH.COOH = H_2O + C_6H_5CH:CH.COOH.$$

It causes a considerable leucocytosis in experimental animals (rabbits), and also in man. It was thus thought that valuable results might be obtained in tuberculous disease by increasing phagocytosis. The clinical results have not been altogether satisfactory, and the treatment has never been at all generally adopted, at any rate in this country; of 903 cases collected from the literature 41 per cent. died or were unaffected.

Based on the salol principle a large number of esters of this acid have been introduced into pharmacology. Thus the 1:3-cresol ester, **Hetocresol,** $C_6H_5CH:CH.CO.OC_6H_4.CH_3$, is an insoluble

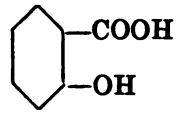
powder intended for use as a local application to tuberculous sinuses, &c.

The guaiacol ester, **Styracol**, $C_6H_5CH:CH.CO.OC_6H_4.OCH_3$, is tasteless, and is said to liberate 85 per cent. of guaiacol in the body. It is intended as a substitute for that drug, and to combine the supposed advantages of cinnamic acid.

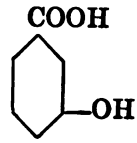
Physiological Effects produced by Entrance of the Carboxyl Radical into the Nucleus of Phenol.

When a carboxyl group is introduced into the phenol nucleus, the physiological reaction of the resulting substance depends on the relative positions of the two substituents; in all three isomers, however, a very great drop in toxicity is noticed.

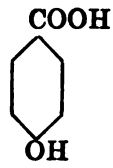
When the two groups are next to each other, i.e. 1:2-oxybenzoic or salicylic acid,



the resulting substance has antiseptic properties closely allied to phenol, and at the same time other characteristics appear which are barely noticeable, if at all, in the hydroxyl substance itself. Thus salicylic acid has an antipyretic action, and more particularly a specific action in rheumatism. On the other hand, both 1:3-oxybenzoic acid,



and the 1:4 derivative,



have entirely lost all the physiological characteristics of phenol, and have neither the antiseptic nor the therapeutic action of salicylic acid, the *ortho* derivative.

When the hydrogen atom of the hydroxyl group is replaced by methyl,

$$C_6H_4\begin{cases}OCH_3\\COOH,\end{cases}$$

the physiological action of the 1 : 2 derivative is very much weaker than salicylic acid itself, it has only slight antiseptic and antipyretic action, and, in the case of animals, is only toxic in large doses. The corresponding 1 : 4 derivative, anisic acid, has no pharmacological reaction at all, and passes unchanged through the organism.

Whereas the introduction of a methyl group into the nucleus of phenol tends to lower the toxicity, whilst raising the antiseptic power, the result in the case of salicylic acid is as follows:—

Ortho-homosalicylic acid (β-cresotinic acid)

$$C_6H_3\begin{cases}OH & 1\\COOH & 2\\CH_3 & 6\end{cases}$$

is physiologically the most reactive, and in relatively small doses produces a paralysis of the muscles of the heart, *para*-homosalicylic (α-cresotinic acid)

$$C_6H_3\begin{cases}OH & 1\\COOH & 2\\CH_3 & 4\end{cases}$$

has less reaction than salicylic itself, whereas *meta*-homosalicylic

$$C_6H_3\begin{cases}OH & 1\\COOH & 2\\CH_3 & 3\end{cases}$$

produces no pharmacological reaction.

The oxynaphthoic acids have a similar action to salicylic acid, but though more powerful they are also caustic, and in doses of 1·5 gm. produce fatal results in rabbits.

A. SALICYLIC ACID AND ITS DERIVATIVES.

Salicylic acid occurs in the free state in buds of *Spiraea ulmaria*, and as methyl ester in oil of *Gaultheria procumbens* (oil of wintergreen).

It may be prepared by the action of carbon dioxide on sodium phenate at a temperature of 180°–220°,

$$2C_6H_5ONa + CO_2 = C_6H_4\begin{cases}ONa\\COONa\end{cases} + C_6H_5OH.$$

This reaction may be modified by saturating sodium phenate with carbon dioxide under pressure, when sodium phenyl carbonate results,

$$C_6H_5ONa + CO_2 = CO\begin{matrix}ONa\\OC_6H_5\end{matrix}.$$

This substance, heated to 120°–130° under pressure, undergoes intramolecular change to sodium salicylate,

$$CO\begin{matrix}ONa\\OC_6H_5\end{matrix} \rightarrow C_6H_4\begin{matrix}OH\\COONa\end{matrix}.$$

Salicylic acid has a sweet, acid taste, and in this form only has antiseptic action. Its sodium salt is a crystalline powder with an unpleasant, sweet taste; it is decomposed by mineral acids, and hence also in the stomach, with the liberation of the free acid.

Both salicylic acid and its sodium salt have objectionable secondary actions—deafness, tinnitus aurium, headache, delirium, haematuria, albuminuria, &c.

In order to overcome these objectionable properties a large variety of salicylic acid derivatives have been prepared and many introduced into pharmacy. Nencki was the first to lead the way into this new field of pharmacodynamics, and to combine together, in the form of esters, two physiologically reactive components. He found that, in spite of the toxicity of these components, the slow breakdown of the esters in the organism led to derivatives of relatively slight toxicity. Such esters, generally possessing hardly any taste and no caustic action, pass unchanged through the stomach, and are decomposed in the duodenum by the action of alkali and enzymes. The acid formed by this saponification is neutralized by the alkali, and the physiological action of the phenol, which is slowly and continuously liberated, commences by reabsorption from that region. From this point of view the so-called 'salol principle' has been already alluded to in the previous pages on phenolic substances and their derivatives.

If it is desired to obtain only the pharmacological reaction of the acid, then clearly it must be combined with an hydroxyl derivative which itself possesses little or no physiological activity; that is, preferably an aliphatic alcohol or an allied substance.

Salicylic acid, owing to the presence of the hydroxyl as well as the carboxyl groups, can play the part of both phenol and acid, and the derivatives employed in medicine may be classified as follows:—

I. Those formed by replacement of hydrogen atom of carboxyl group, substances of general formula

$$1:2\ C_6H_4\begin{cases}OH\\COOR\end{cases}$$

These are further subdivided according to the nature of the radical R, viz.: (*a*) Those in which R is of an aliphatic nature, i. e. physiologically inactive, and (*b*) those in which the radical is of a phenolic, and, hence, antiseptic nature.

II. Those derivatives formed by replacing hydrogen of the hydroxyl group, of general formula

$$1:2\ C_6H_4\begin{cases}OX\\COOH\end{cases}$$

X cannot be the radical of aliphatic alcohols for reasons previously given (p. 151), but must be of a type which will be easily broken down in the organism with the liberation of free salicylic acid.

III. Derivatives in which both hydrogen atoms have been replaced,

$$1:2\ C_6H_4\begin{cases}OX\\COOR\end{cases}$$

Subdivided in this manner, it will be noticed that Class I (*a*) and Class II contain closely allied substances, i. e. derivatives whose physiological action is very similar to salicylic acid itself.

Class I (a).

Methyl salicylate,

$$C_6H_4\begin{cases}OH\\COOCH_3\end{cases},$$

(**oil of wintergreen**), can be given internally as an emulsion or in milk in 10–20 minim doses. It is very active, has not the unpleasant sweet taste of sodium salicylate, but is often very irritating to the stomach. Applied externally, it is useful in acute muscular rheumatism.

Ethyl salicylate,

$$C_6H_4\begin{cases}OH\\COOC_2H_5\end{cases},$$

was investigated owing to the fact that ethyl derivatives are often less harmful than the corresponding methyl. According to Houghton, it is only half as toxic as the previously mentioned substance.

The monoglycerin ester of salicylic acid, **Glycosal**,

$$C_6H_4\begin{matrix}OH\\ \diagup\\ \diagdown\\ COO.C_3H_5(OH)_2,\end{matrix}$$

is obtained by the action of condensing agents, such as 60 per cent. sulphuric acid on a mixture of salicylic acid and glycerin. The triglycerin ester has also been investigated, but is found to be reabsorbed to nothing like the same extent as the mono derivative, of which about 96 per cent. undergoes that process.

It is a crystalline powder, slightly soluble in water, more so in alcohol and glycerin. It possesses no odour, and is intended for internal and external use. Externally it is not irritating, and is fairly rapidly absorbed, appearing in the urine about six hours after a solution in alcohol has been painted on the skin.

The methoxymethyl ester of salicylic acid, **Mesotan**,

$$C_6H_4\begin{matrix}OH\\ \diagup\\ \diagdown\\ COO.CH_2.O.CH_3,\end{matrix}$$

was introduced by Floret in 1902, and is obtained by the action of chlormethyl ether on sodium salicylate,

$$C_6H_4\begin{matrix}OH\\ \diagup\\ \diagdown\\ COONa\end{matrix} + Cl.CH_2.O.CH_3 = NaCl + C_6H_4\begin{matrix}OH\\ \diagup\\ \diagdown\\ COO.CH_2.O.CH_3.\end{matrix}$$

It is unstable, and very readily breaks down in presence of water into formaldehyde, a reaction probably expressed by the following reaction:—

$$C_6H_4\begin{matrix}OH\\ \diagup\\ \diagdown\\ COO.CH_2.O.CH_3\end{matrix} + H_2O = C_6H_4\begin{matrix}OH\\ \diagup\\ \diagdown\\ COOH\end{matrix} + H.CHO + CH_3OH.$$

It is used as a local application to painful joints in acute rheumatism and similar conditions. It has been observed to produce dermatitis, and should therefore be employed in weak dilutions, and in media not easily absorbed, e.g. vaseline or olive oil. The preparation is unstable.

Acetol-salicylic ester, **Salacetol**,

$$C_6H_4\begin{matrix}OH\\ \diagup\\ \diagdown\\ COO.CH_2.CO.CH_3,\end{matrix}$$

is obtained by the action of chloracetone on sodium salicylate,

$$C_6H_4\langle^{OH}_{COONa} + Cl.CH_2.CO.CH_3 = NaCl + C_6H_4\langle^{OH}_{COO.CH_2.CO.CH_3}.$$

Like the previous compound, it is very readily saponified, so much so that the secondary action of salicylic acid may appear almost as quickly as in the case of the free acid itself.

Salen is a mixture of methyl and ethyl glycolic acid esters of salicylic acid,

$$C_6H_4\langle^{OH}_{COOCH_2COOCH_3} \text{ and } C_6H_4\langle^{OH}_{COOCH_2COOC_2H_5}.$$

These substances are crystalline, and have melting-points between 28°–29° C. and 38°–39° C. respectively. When mixed, however, they liquefy, and do not become solid till raised to a temperature of 5°–10° C. The mixture is soluble in alcohol, castor oil, or a mixture of olive oil and chloroform. It is inodorous, and is intended to replace oil of wintergreen as a local application.

Class I (b).

One of the simplest representatives of this group is the phenyl ester of salicylic acid, or **Salol,**

$$C_6H_4\langle^{OH}_{COO.C_6H_5}.$$

It results on heating the acid itself to 200–220° with the elimination of water and carbon dioxide,

$$2C_6H_4\langle^{OH}_{COOH} = H_2O + CO_2 + C_6H_4\langle^{OH}_{COOC_6H_5},$$

or it may be obtained by the action of phosphorus oxychloride on a mixture of salicylic acid and phenol,

$$C_6H_4\langle^{OH}_{COO\,H} + OH\,C_6H_5 = H_2O + C_6H_4\langle^{OH}_{COOC_6H_5}.$$

Both the toxicity and the intestinal antiseptic action of salol are due to the phenol group. The sodium salicylate is not antiseptic (p. 16), and is much less toxic than phenol. The salol compounds are unsuited for wound dressings, as they are only split up with difficulty by the body fluids. When the specific action of the salicylate is required, a compound which on decomposition yields some indifferent body should be employed.

In place of phenol, the following and many other similar hydroxyl substances may be combined with salicylic acid through the agency of phosphorus oxy-chloride:—

1. α- and β-naphthol . . . $C_6H_4\langle^{OH}_{COOC_{10}H_7}$
2. 1 : 2-, 1 : 3-, 1 : 4-cresol . . $C_6H_4\langle^{OH}_{COOC_6H_4.CH_3}$
3. Thymol . . . . . $C_6H_4\langle^{OH}_{COO.C_{10}H_{13}}$
4. One molecule of resorcin giving $C_6H_4\langle^{OH}_{COO.C_6H_4.OH}$

   Two „ „ „ $C_6H_4\langle^{O.COC_6H_4.OH}_{O.COC_6H_4OH}$

   or the corresponding methoxy derivatives . . . $C_6H_4\langle^{OH}_{COO.C_6H_4OCH_3}$
5. Guaiacol . . . . $C_6H_4\langle^{OH}_{COOC_6H_4OCH_3}$
6. The mixture of phenols called creosote.
7. 1 : 4-nitrophenol . . . $C_6H_4\langle^{OH}_{COO.C_6H_4.NO_2}$
8. Gaultheria oil . . . $C_6H_4\langle^{OH}_{COO.C_6H_4.COOCH_3}$
9. Gallic acid . . . . $C_6H_4\langle^{OH}_{CO.O.OC.C_6H_2(OH)_3}$

In place of salicylic acid, the inert anisic acid,

$$C_6H_4\langle^{OCH_3}_{COOH}\ 1:4,$$

may be used to carry physiologically active phenols in the form of their respective esters. Thus the anisic acid derivatives, among others, of the following have been prepared:—

1. Phenol . . . . . $C_6H_4\langle^{OCH_3}_{COOC_6H_5}$
2. Guaiacol . . . . $C_6H_4\langle^{OCH_3}_{COO.C_6H_4.OCH_3}$
3. Creosol . . . . . $C_6H_4\langle^{OCH_3}_{COO.C_7H_6.OCH_3}$

and salicylic acid has been replaced by the homosalicylic acids.

The above examples show the large number of permutations and combinations which can be made between acids and hydroxyl-containing substances; they are all decomposed like salol, for example, and substances with novel pharmacological action cannot be looked

for in this group. One may have an advantage over another as regards taste or solubility or the ease with which it breaks up in the duodenum and so allows its physiological reaction to appear. It will be evident that there are possibilities enough to enable fresh derivatives of this type to be continually placed on the market, although the probability of these possessing advantages over the older preparations is but slight.

An example is given by Fränkel of the manner in which a drug may be introduced, although its constitution would indicate at once that it is valueless. Thus 1 : 2-methoxy or ethoxybenzoic acid on nitration gives a 5-nitro derivative,

$$C_6H_3\begin{cases}COOH & 1\\ O.CH_3 & 2\\ NO_2 & 5\end{cases}$$

This was reduced and converted into the corresponding acetyl derivative by means of acetic anhydride,

$$C_6H_3\begin{cases}COOH\\ OCH_3\\ NH(COCH_3).\end{cases}$$

Now such a substance would neither have the phenacetin reaction, owing to the presence of the carboxyl group, nor the physiological action of salicylic acid, since it does not contain the free hydroxyl group.

In this group of salicylic acid derivatives salicyl-acetyl-*p*-amidophenol ether, or **Salophen,**

$$C_6H_4\begin{cases}OH\\ COO.C_6H_4.NH(COCH_3),\end{cases}$$

may be mentioned; it can be obtained by the reduction of the *p*-nitrophenol ester of salicylic acid, followed by the conversion of the amido substance into its acetyl derivative. It is almost insoluble in water, and has no taste or smell, and is of small toxicity, but on decomposition in the organism it gives rise to 1 : 4-acetylamido phenol,

$$C_6H_4\begin{cases}OH\\ NH(COCH_3),\end{cases}$$

a substance possessing but very slight antiseptic action, and more nearly related, in its physiological action, to the aniline antipyretics than to phenol. It is unaffected by pepsin, but decomposed in the small intestine. Its antipyretic action is feeble, but it may be employed for the salicyl action in acute rheumatism.

Class II.

Acetyl-salicylic acid, or **Aspirin,**

$$C_6H_4\begin{cases}O(CH_3CO)\\COOH\end{cases}$$

was introduced by Dreser in 1899 as a substitute for salicylic acid. It is obtained by the action of acetic anhydride or acetyl chloride on salicylic acid at high temperatures. It is largely used instead of sodium salicylate in acute rheumatism. It is thought to be better tolerated by the stomach, and only rarely gives rise to unpleasant symptoms. Erythema and pruritus have occasionally been observed.

Salicyl-acetic acid,

$$C_6H_4\begin{cases}O.CH_2COOH\\COOH\end{cases}$$

is obtained by acting upon the sodium salt of the anilide,

$$C_6H_4\begin{cases}ONa\\CO.NHC_6H_5,\end{cases}$$

with the sodium salt of chloracetic acid :—

$$C_6H_4\begin{cases}ONa\\CONHC_6H_5\end{cases} + Cl.CH_2COONa = C_6H_4\begin{cases}O.CH_2COONa\\CONHC_6H_5\end{cases} + NaCl.$$

On heating with alkalis this is decomposed :—

$$C_6H_4\begin{cases}O.CH_2COONa\\CONHC_6H_5\end{cases} + NaOH = C_6H_4\begin{cases}O.CH_2COONa\\COONa\end{cases} + C_6H_5NH_2.$$

Class III.

Acetyl salicylic methyl ester, **Methyl rhodin,**

$$C_6H_4\begin{cases}O(COCH_3)\\COOCH_3\end{cases}$$

is a colourless crystalline substance, not affected by dilute acids, and consequently undecomposed in the stomach. It is stated to be better adapted for patients with enfeebled digestion than sodium salicylate.

Benzosalin is the methyl ester of benzoyl salicylic acid,

$$C_6H_4\begin{cases}O(COC_6H_5)\\COO.CH_3\end{cases}$$

it is not decomposed till it reaches the small intestine, and does not split off phenol, but, beyond this, it appears to possess no particular advantages over other salicyl compounds.

B. TANNIC ACID AND ITS DERIVATIVES.

The tannic acids, or tannins, occur widely distributed in the vegetable kingdom. They are soluble in water, and form compounds with gelatin and with animal hides, and are consequently employed in the manufacture of leather. They also precipitate protein solutions. Some appear to be glucosides of gallic acid, $(OH)_3 . C_6H_2 . COOH$, and, on boiling with dilute acids, give grape sugar and gallic acid; others contain phloroglucin in place of sugar. Pure tannic acid, however, appears to be a digallic acid, since on warming with dilute acids or alkalis it gives rise to that acid alone.

Like salicylic acid, it has antiseptic properties; its main property is due to its local action on protoplasm, and is known as 'astringency'. It appears in the urine partly as gallic acid and pyrogallol; in some cases, apparently, some tannic acid is passed unchanged, in others as a sulphuric ester. But tannic acid has two characteristics which stand in the way of its employment as an intestinal disinfectant. Firstly, it possesses an objectionable taste, and, secondly, it loses its antiseptic property in the stomach, owing to its combining with protein bodies in its contents or mucous membrane. Consequently, it is necessary to obtain derivatives which can pass unchanged through that organ, but will be decomposed, like salol, in the duodenum. For this purpose various acetyl derivatives have been investigated, and it has been found that the triacetyl tannic acid and those substances containing more acetyl groups are not decomposed by the intestinal juice, and consequently have not the required action.

When tannic acid is treated with a mixture of acetic acid and acetic anhydride, however, a mixture of mono- and di-acetyl tannic acid results, which H. Meyer and F. Müller introduced into pharmacy in 1894 under the name of **Tannigen,** $C_{14}H_8(COCH_3)_2O_9$. This body is insoluble in water, and consequently tasteless. It is dissolved by alkalis and precipitated by acids. At body temperature it forms a sticky mass in presence of water, but it can be obtained in tablets which obviate this disadvantage. Both this and the next mentioned body appear in the urine as gallic acid.

In another direction tannic acid derivatives have been obtained by combination with albuminous substances. Gottlieb and others precipitated egg albumen with the acid, but the resulting compound is decomposed in the stomach. If, however, it is heated for 6–10 hours at 110° C., it loses this property, and is not broken down into

its constituents until it reaches the duodenum. This preparation goes by the name of **Tannalbin**; it contains 50 per cent. of tannin. A similar preparation is named **Honthin.** Other preparations of this type can be obtained by precipitating gelatine solutions with tannic acid (**Tannocol**), or with casein (**Tannocase**). These bodies fulfil their purpose, but considering what their purpose was, it seems not a little curious that they should be seriously recommended in diseased conditions of the lower bowel to be given *per rectum.*

The combination of an antiseptic substance, formaldehyde, with tannic acid is methylene ditannic acid, or **Tannoform,**

$$CH_2\begin{matrix}C_{14}H_9O_9\\C_{14}H_9O_9\end{matrix}$$

obtained by the action of hydrochloric acid on a solution of formaldehyde and tannic acid, or by heating the components under pressure.

It is only slightly soluble in water, soluble in alcohol, and devoid of odour. It appears to be mainly useful as an external application.

Tannic acid has also been combined with hexamethylene tetramine, and the resulting substance is termed **Tannopin** or **Tannon,**

$$(CH_2)_6N_4(C_{14}H_{10}O_9)_3,$$

but this body will not liberate so much formaldehyde, and consequently will not have so powerful an antiseptic action as the direct compound of tannin and formalin. It is only broken down in alkaline solutions, and is intended for use as a urinary disinfectant.

Tannal is a tannate of aluminium, it is insoluble in water, and has the formula $Al_2(OH)_4(C_{14}H_9O_9)_2 + IOH_2O$.

NOTE.—With regard to the clinical value of these two classes of derivatives, it may be remarked that sodium salicylate will probably be found quite as efficacious and suitable as any of the newer products in the very large majority of cases. When this body is not well tolerated by the stomach, that is if nausea or vomiting occurs, salicin, the glucoside (see p. 322), may be tried or acetyl salicylic acid. General toxic symptoms are met by either diminishing the dose or by giving some preparation which is less rapidly and completely absorbed or contains a smaller proportion of the active principle.

As to the tannic acid substitutes those combined with protein in some form or other appear to be the most scientifically justifiable.

CHAPTER VIII

ANTISEPTIC AND OTHER SUBSTANCES CONTAINING IODINE AND SULPHUR.—Iodoform. Classification of substances introduced in place of Iodoform and the Alkali iodides. Derivatives containing Sulphur—Ichthyol.

ANTISEPTICS CONTAINING IODINE.

I. Iodoform and Substances of Allied Physiological Action.

IODOFORM, CHI_3, was the first solid antiseptic introduced into pharmacy. It may be obtained by the action of iodine, in the presence of the alkalis, on a large number of aliphatic derivatives, such as ethyl alcohol, acetone, acetaldehyde, &c. It is generally prepared by adding iodine to a warm solution of either soda or potash in dilute alcohol or acetone; the iodoform formed separates out and is filtered off. The solution contains alkaline iodides and iodates; on the addition of a further quantity of alcohol (or acetone) and the passage of a slow stream of chlorine through the solution (resulting in the liberation of free iodine), a further quantity of iodoform separates out.

It may also be obtained by the electrolysis of a solution of alcohol (or acetone) containing potassium iodide, whilst a slow stream of carbon dioxide is being passed through it.

It is unnecessary to describe the characteristic properties of this well-known substance. As such, it is not an antiseptic, and its action depends on the liberation of free iodine by the action of the secretions of the wound upon which or in which it is used. Owing to its physical characteristics (it melts at 120° and volatilizes readily at medium temperatures) it cannot be sterilized by heat.

Iodoform possesses two great disadvantages—firstly, its objectionable smell, and, secondly, the fact that it may be absorbed from wounds and consequently give rise to toxic symptoms. Various attempts have been made to overcome these objections to its use, and three classes of compounds have been produced as substitutes :—

A. Unstable compounds or mixtures of iodoform with various substances tending to destroy or lessen its smell.

B. Insoluble and unstable iodine derivatives.

C. Derivatives of totally different type to iodoform itself, but which, like it, liberate iodine and consequently have a similar physiological action.

Class A.

To this group belongs **iodoformin,** $(CH_2)_6N_4.CHI_3$, an addition product of hexamethylene tetramine and iodoform, but this compound has always a slight smell of the latter substance, owing to the ease with which it is broken down into its constituents by moisture. It contains 75 per cent. iodoform.

Iodoformal, although not a derivative of iodoform, may be mentioned in this place. It is the hydriodide of hexamethylene, and is said to possess higher antiseptic power than iodoform. Its action probably depends on its dissociation into hexamethylene and hydriodic acid, this latter substance being readily decomposed, giving free iodine.

Various tannic acid and albuminous preparations of iodoform have been put on the market, such for instance as **iodoformogen,** an almost odourless compound with albumen, which may be sterilized at 100° and is stated not to give rise to iodine-eczema as readily as does iodoform itself. But many substances of this type are merely mixtures, and will not further be described.

Class B.

Various unstable compounds of iodine and albumen or glutinous substances have been introduced. That which goes by the name of **Iodolene** is an iodo derivative of albumen. It is a yellow powder insoluble in the ordinary solvents.

Iodyloform is a preparation of iodine and a glutinous substance; it is a yellowish-brown odourless powder insoluble in water and containing 10 per cent. of iodine. Sperling states that it is equivalent to iodoform in disinfecting power, but is less efficacious in the treatment of wounds.

Iodeigon and **peptoiodeigon** are compounds of iodine with protein; the former is insoluble in water, the latter soluble.

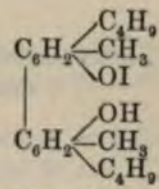
Class C.

It is necessary that an iodoform substitute should be an insoluble solid, possessing antiseptic properties, but have no smell and only [illegible]ticity. Since the characteristic action of iodoform is due

to the liberation of iodine, this property has been retained in all the substances hitherto introduced to supersede it. In fact the aim of the manufacturers has been to produce easily decomposed iodine derivatives, and, so far, no other element or radical has been found that will satisfactorily replace iodine, although attempts have been made with sulphur, which will be described later.

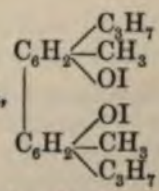
The entrance of iodine into aliphatic and aromatic substances is generally followed by a rise in antiseptic power, but derivatives of the first type are usually sufficiently stable to resist decomposition by the wound secretions. It was but natural that the antiseptic phenols should be investigated in the hope of obtaining suitable substitutes, but again, when the hydrogen of the nucleus is replaced by iodine, the stability of the resulting iodo-phenols is too great, and although they possess powerful antiseptic properties, they can in no sense of the word be regarded as iodoform substitutes. On the other hand, those phenolic derivatives in which the hydrogen of the hydroxyl group is replaced by iodine are readily decomposed with the liberation of the halogen, and have consequently been introduced into pharmacy. Of these the two following are the most important:—

Di-*iso*-butyl-*o*-cresol iodide or **Europhen,**



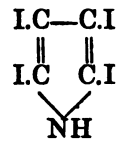
Iso-butyl-*o*-cresol is obtained by the action of condensing agents on a mixture of *o*-cresol and *iso*-butyl alcohol; when iodine acts on an alkaline solution of this substance europhen results. It is a yellow, light powder, keeps well when dry, and in contact with moisture slowly gives off free iodine. It is said to be valuable for syphilitic cases.

Di-thymol-di-iodide, **Aristol,** or **Annidalin,**



was introduced by Eichkoff in 1890, and may be obtained by the action of iodine on an alkaline solution of thymol. It is a brick-red powder, insoluble in water, and is said to be a useful application for wounds.

Belonging to a different class from the previous compounds is tetra-iodo-pyrrol or **Iodol,**



It is obtained by the action of iodine on alkaline solutions of pyrrol, or by firstly obtaining tetrachlorpyrrol by the action of chlorine on pyrrol, and then decomposing this derivative with potassium iodide,

1. $C_4H_4 . NH + 8Cl = 4HCl + C_4Cl_4 . NH$

2. $C_4Cl_4 . NH + 4KI = 4KCl + \underset{\text{Iodol.}}{C_4I_4 . NH}.$

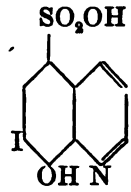
The physiological action of iodol, which is a tasteless and odourless powder, is very similar to that of iodoform, but it adheres better to the epidermis and the surface of wounds. It has also been used as a substitute for potassium iodide, as one-half of the iodine reappears in the urine, showing that it is broken up in the body.

II. Iodine-containing Antiseptics not liberating that element in the organism.

The following derivatives owe their increased antiseptic power to the replacement of hydrogen by iodine, but, unlike the previously mentioned substances, iodine is not liberated.

Quinoline, as well as 1-oxyquinoline, has marked antipyretic and antiseptic properties, and the latter characteristic is increased by the replacement of hydrogen by iodine. Based on this, the following two compounds have been introduced into pharmacy:—

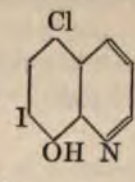
Quinoline-1-oxy-2-iodo-4-sulphonic acid or **Loretin,**



This is obtained from 1-oxyquinoline by the action of cold fuming sulphuric acid; the sodium salt of the resulting sulphonic acid is then treated with iodine. It is a yellow, tasteless, insoluble powder,

and when mixed with sodium bicarbonate goes by the name of **Griserin.** It is used in tuberculosis and other infectious diseases.

1-oxy-2-iodo-4-chlor-quinoline or **vioform,**



was introduced in 1900 by E. Tavel and Tomarkim.

1-oxyquinoline is chlorinated, and the resulting substance acted upon by iodine in potassium iodide solution. It is a greyish-yellow tasteless powder, insoluble in water, and without smell; it may be sterilized by heating to 100°, at higher temperatures decomposition sets in. It is stated to have a more powerful action than iodoform.

The iodine derivatives of 1 : 4-phenol sulphonic acid were investigated by Ostermayer in 1880, and introduced under the name of **Sozoiodol** preparations. When phenol is acted upon by warm sulphuric acid the chief product is *p*-phenol sulphuric acid,

$$C_6H_4\begin{matrix}OH\\SO_2OH.\end{matrix}$$

When a solution of the potassium salt of this acid is treated with chloride of iodine, the di-iodide of *p*-phenol sulphonate of potash is formed,

$$C_6H_4\begin{matrix}OH\\SO_2OK\end{matrix} + 2ICl = C_6H_2I_2\begin{matrix}OH\\SO_2OK\end{matrix} + 2HCl.$$

The free acid may be obtained by the action of sulphuric acid upon the barium salt; it goes by the name of **Sozoiodolic acid,**

$$C_6H_2I_2\begin{matrix}OH\\SO_2OH\end{matrix} + 3H_2O,$$

and is soluble in water and alcohol.

The sodium salt is more soluble in water than the potassium; with the exception of the mercury compound all the salts are more or less soluble in that medium.

The sozoiodol preparations pass unchanged through the organism, and it is difficult to imagine that they possess any pronounced action. Phenol has antiseptic properties, but the introduction of the sulphonic group results, as is the invariable rule, in a decrease in physiological characteristics; and although the introduction of iodine atoms into the molecule of this substance tends to raise the

antiseptic power, it cannot do so to any great extent in a substance possessing such powerful acid properties as phenol sulphuric acid. Frinkel remarks that it is only the zinc and mercury salts which are of value, and in all probability these owe their reactivity not to the acid (sozoiodol) radical, but to the metallic ion.

Iodo-anisol, $C_6H_4\begin{cases}OCH_3\\IO_2\end{cases}$

was introduced in 1904, and is obtained from the 1 : 4-iodanisol,

$$C_6H_4\begin{cases}OCH_3\\I\end{cases}$$

by the action of chlorine, which gives rise to

$$C_6H_4\begin{cases}OCH_3\\ICl_2\end{cases}$$

On treatment with caustic alkali this iodochloride gives iodoso-anisol,

$$C_6H_4\begin{cases}OCH_3\\IO\end{cases}$$

and when this is boiled with water the following decomposition takes place :—

$$2C_6H_4\begin{cases}OCH_3\\IO\end{cases} = C_6H_4\begin{cases}OCH_3\\I\end{cases} + C_6H_4\begin{cases}OCH_3\\IO_2\end{cases}$$

It is an explosive substance, only slightly soluble in cold water, and is used mixed with an equal quantity of calcium phosphate, or made into a paste with glycerin. It behaves like a superoxide, and to this may possibly be ascribed its action; if this is the case it may be compared to benzoyl peroxide $(C_6H_5CO)_2.O_2$, which has also been recommended as a useful antiseptic; it may be applied locally as a powder, and does not give rise to symptoms of irritation owing to its mild anaesthetic effect.

Losophane is a tri-iodo derivative of 1 : 3-cresol,

$$C_6HI_3\begin{cases}OH\\CH_3\end{cases}$$

It contains 80 per cent. iodine. It is a crystalline powder soluble in alcohol, oil, &c., and has been used in parasitic skin diseases. It is, however, too irritant to be of much value.

…en is tetra-iodo phenolphthalein. It is insoluble in water … slightly soluble in alcohol. It has a slight odour like …dine, of which it contains 60 per cent. It is used as …owder. Internally, it is said to pass through the system

unchanged. **Antiosin** is its sodium salt and **Eudoxin** its bismuth salt. The former is soluble in water, and is a non-toxic external antiseptic; the latter is insoluble, and intended for use in putrefactive conditions of the gastro-intestinal tract.

The proportion of iodine in various preparations is shown in the following table, modified from one given in Martindale and Westcott's extra *Pharmacopoeia* (10th edition):—

Iodine easily liberated.		Iodine not liberated.		Pass unchanged through animal organism.	
	per cent.		per cent.		per cent.
Iodoform	96·6	Losophen	80·0	Sozoiodol	50·0
Iodol	90·0	Di-iodo salicylic acid	66·67		
Aristol	50·0	Iodo salicylic acid	50·0		
Europhen	28·5				

ORGANIC SUBSTANCES INTRODUCED IN PLACE OF THE ALKALI IODIDES.

The objectionable, and occasionally very inconvenient, characteristics of potassium iodide have led to the investigation of many non-toxic iodine-containing organic substances. It is clear that to bring about the same physiological reaction as the alkaline iodides, these organic derivatives must be decomposed in the body, and that consequently the only difference between them will be that, instead of the rapid absorption of the former, a slower process will take place, dependent on their stability, or the ease with which the organic derivative is broken down in the system.

On lines similar to those previously indicated with other bodies, iodine has been combined with protein matter, and one of such bodies—

Iodalbin, contains 21·5 per cent. of that element. It passes unchanged through the stomach, and is decomposed in the intestinal canal; the reabsorption of iodine commences from that region.

Iodipin is a preparation formed by the addition of iodine to unsaturated oils; of the latter, oil of sesame is said to be the best, on account of the ease with which it is digested and its freedom from taste. Two varieties of this preparation are on the market, one containing 10 per cent. iodine and suitable for internal administration, and the other 24 per cent. specially useful for injections.

It appears to be a most reliable substitute for potassium iodide, and is most useful for subcutaneous injections, in which case iodine is only slowly excreted by the urine.

According to Lesser, patients may be accustomed to the use of iodides by means of subcutaneous injections of this derivative.

Experiments have shown that iodipin, when subcutaneously injected, remains for a long time at the seat of injection, and only slowly becomes absorbed by the tissues in the form of potassium iodide. Its diffusion throughout the body is shown by the fact that iodine was detected in the epithelial scales of a syphilide during the administration of the drug.

Iothion is di-iodo-hydroxy-propane, $CH_2I.CHI.CH_2OH$, and though it cannot be used internally or hypodermically, it is intended as a substitute for potassium iodide, the method of administration being by inunction.

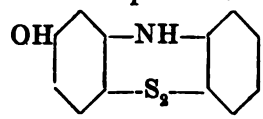
SUBSTANCES CONTAINING SULPHUR.

Sulphur itself, though an inert body, is, like iodoform, capable of producing antiseptic effects when it is brought in contact with fresh tissues. It has been employed instead of iodoform in surgery for packing suppurating cavities and for other purposes; the tissues round are blackened and slough away, and a strong smell of sulphuretted hydrogen is observed, which would indicate a reducing process. Lane, who was the first to employ it in this way in 1893, thinks the action is due to the formation of sulphurous acid, which is subsequently oxidized to sulphuric acid. A powerful reaction appears to take place, and, as a rule, it is unsafe and unnecessary to leave the sulphur in contact with the tissues for more than 24 hours.[1]

Organic sulphur derivatives in which sulphur is in the divalent and hence unoxidized condition have mild antiseptic action, combined with the property of promoting the formation of granulation tissue, and consequently many attempts have been made to arrive at substances which might have a corresponding action to iodoform, but so far without any marked success.

Thus thio-resorcin, $C_6H_4O_2S_2$, obtained by the action of sulphur on a solution of resorcin in potash, cannot be employed owing to the cutaneous irritation which it produces.

Sulphaminol,



prepared from oxy-diphenyl-amine, has not proved of value.

A combined sulphur and iodine derivative is the ethyl iodide

[1] *Med. Chi. Trans.*, vol. 78.

addition compound of allyl urea (see thiosinamine, p. 218) which goes by the name of **Tiodine,**

$$CS\begin{matrix}\diagup NHC_3H_5\\ \diagdown NH_2C_2H_5I.\end{matrix}$$

This is a crystalline substance soluble in water in all proportions, and readily absorbed by the organism when taken by the mouth or hypodermically. In therapeutic doses it is said to be absolutely non-toxic.

ICHTHYOL.

The most commonly employed organic sulphur compound is perhaps that known as ichthyol, whose chemical constitution has not yet been determined. It is a bituminous product containing about 15 per cent. of sulphur. Ordinary medicinal ichthyol is sulphoichthyolate of ammonia, but corresponding preparations of lithium, sodium and zinc are manufactured. Owing to the unpleasant smell and taste of ichthyol, numerous modifications of the original substances have been prepared. **Desichthyol** is prepared by the action of superheated steam on ichthyol, and is tasteless. A combination with albumin, **Ichthalbin,** is insoluble, and consequently has neither taste nor odour.

Ichthoform is prepared by the action of formaldehyde, and though tasteless, is only very slightly soluble in alkaline fluids, so that internally its action is slow.

Various salts of the sulphonic acid have been introduced, such as: **Ferrichthyol,** the iron derivative, and **Ichthargan,** the silver salt. **Anytols** are compounds of phenols with **anytin,** the ammonia salt of a hydrocarbon sulphonate, obtained with ichthyol and containing 33 per cent. of ichthyol sulphonic acid.

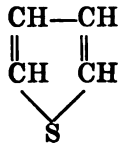
Various bodies have also been prepared which closely resemble ichthyol. **Thiol** is a mixture of sulphonized hydrocarbons, and is obtained by heating gas oil with sulphur. **Tumenol** and **petrosulphol** are similar preparations. Blubber and lanolin have also been combined with sulphur; and lysol, when treated with sulphur, becomes converted into a dark brown mass, soluble in water, and showing some of the properties of ichthyol. All these bodies of unknown constitution are empirical imitations of the natural product, which is also of unknown chemical constitution; but, besides these, a large number of pure chemical substances have been suggested as likely to have the same therapeutic value as ichthyol without its aesthetic disadvantages. Alkyl sulphides, disulpho-

cyanide of potassium, alkyl-thio-urea, thio-dinaphthyol-oxide, thio-biazol derivatives, and various other sulphur compounds have all been tried and found wanting.

Fränkel has formulated the essential points on which he considers the therapeutic efficacy of ichthyol depends. These are :—

1. The sulphur must be present in an unoxidized form, firmly combined in the molecule, and not in the form of an easily separated sulphydril group.
2. The compound must be unsaturated.
3. The compound must be cyclic in character.

Fränkel suggests that these conditions are best satisfied by taking as a basis **thiophene,**



certain derivatives of which are stated to correspond very closely to ichthyol in their pharmacological properties.

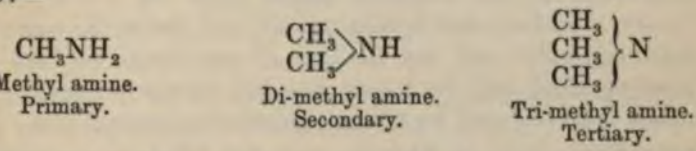
CHAPTER IX

DERIVATIVES OF AMMONIA.—*The Main Group of Synthetic Antipyretics.*—Chemical and physiological character of Aliphatic and Aromatic Amines. Aniline, Acetanilide, and allied substances. Classification and discussion of *para*-Amido-phenol derivatives.

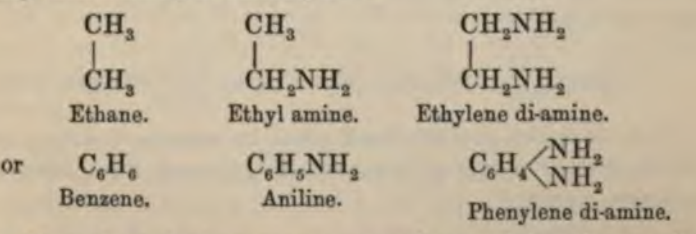
DERIVATIVES OF AMMONIA.

I. THE AMINES.

THE Organic Amines may be regarded as derivatives of ammonia, NH_3, in which the hydrogen atom or atoms have been replaced by alkyl groups; they are distinguished as primary, secondary, or tertiary, according to the actual number of atoms so replaced. Thus:—



The **Primary Amines** are consequently substances in which the hydrogen atom of any hydrocarbon, aliphatic or aromatic, has been replaced by the **Amido** (NH_2) group. Several such radicals can replace hydrogen atoms in the same molecule, and give rise to primary mon-amines, di-amines, &c.:—



The **Secondary Amines** are compounds containing the so-called **Imido** group (NH).

The **Tertiary Amines,** less reactive than the others, have all the hydrogen atoms of the original ammonia replaced by alkyl groups.

They are characterised by their property of uniting with alkyl halogen derivatives, whereby the trivalent nitrogen passes over to the pentavalent condition (see p. 2). The resulting substances may be regarded as ammonium haloids in which the hydrogen atoms are replaced by the alkyl group,

$$NH_3 - HI = NH_4I; \quad (CH_3)_3N + CH_3I = (CH_3)_4N.I$$

Ammonium iodide. Tetra-methyl ammonium iodide.

General Methods employed in the preparation of the Amines.

1. **Primary amines may be obtained by the reduction of the nitriles in alcoholic solution, by means of sodium.**

$$CH_3CN + 4H = CH_3.CH_2.NH_2$$

Methyl nitrile. Ethylamine.

$$C_6H_5CN + 4H = C_6H_5CH_2.NH_2.$$

Benzonitrile. Benzylamine.

2. **The action of ammonia in alcoholic solution on the halogen derivatives of the aliphatic series** gives rise to a mixture of primary, secondary, and tertiary amines, and also of the quaternary ammonium salts, and the isolation of any single product is an operation which will be found described in the textbooks. The method is chiefly used for the preparation of tertiary amines—those most easily isolated—but for the production of primary or secondary the formation of other products is to be avoided; in the former case, instead of ammonia, one of its derivatives, phthalimide, is best employed.

Phthalimide readily gives a potassium derivative, which easily interacts with ethyl iodide, for example, giving the corresponding ethyl phthalimide,

$$C_6H_4\begin{matrix}CO\\CO\end{matrix}\!>\!N.K + I.C_2H_5 = C_6H_4\begin{matrix}CO\\CO\end{matrix}\!>\!N.C_2H_5 + KI.$$

This substance is then decomposed by means of strong hydrochloric acid or alkali, giving phthalic acid and the corresponding primary amine,

$$C_6H_4\begin{matrix}CO\\CO\end{matrix}\!>\!N.C_2H_5 + 2H_2O = C_6H_4\begin{matrix}COOH\\COOH\end{matrix} + C_2H_5NH_2.$$

For the preparation of secondary amines the following indirect

be used.

When aniline, $C_6H_5NH_2$, is treated with ethyl iodide, for instance, the tertiary amine, $C_6H_5N(C_2H_5)_2$, diethylaniline is the product most easily isolated. This substance gives a nitroso-derivative on treatment with nitrous acid,

$$C_6H_5N(C_2H_5)_2 + HNO_2 = H_2O + NO\text{—}C_6H_4\text{—}N(C_2H_5)_2$$

p-nitroso-diethyl aniline.

This, on heating with potash, forms nitroso-phenol and **Diethylamine,**

$$C_6H_4\begin{cases}NO\\N(C_2H_5)_2\end{cases} + H_2O = C_6H_4\begin{cases}NO\\OH\end{cases} + (C_2H_5)_2NH.$$

In the case of the **halogen derivatives of the aromatic series,** no reaction with ammonia, similar to that just described, takes place. It is only when such a substituent as the nitro group has replaced a hydrogen atom in the nucleus in the *o* and *p* position to the halogen, that the characteristic property of the benzene complex is weakened, and ammonia is capable of interacting. When three such groups are present, as for instance in picryl chloride,

$$C_6H_2\begin{cases}NO_2\\NO_2\\NO_2\\Cl\end{cases}$$

the reactivity of the chlorine atom is greatly increased, and ammonia very readily gives rise to the corresponding amine.

$$C_6H_2\begin{cases}(NO_2)_3\\NH_2\end{cases}$$

In the aromatic series, the true analogues of the aliphatic amines are those derivatives containing the amido group in the side-chain, benzylamine, $C_6H_5 . CH_2NH_2$, for instance. This substance, however, may be obtained by the action of ammonia on the corresponding halogen derivative, $C_6H_5CH_2Cl$, that is by a reaction analogous to that which takes place with the aliphatic halogen substitution products.

3. Amido compounds result from the reduction of the nitro derivatives of either aliphatic or aromatic series. But this method of preparation is entirely confined to the latter hydrocarbons, owing to the ease with which the nitro substitution products of this series are obtained. Nitro-benzene, for instance, is reduced to aniline on a commercial scale by means of iron and hydrochloric acid—

$$C_6H_5NO_2 + 6H = C_6H_5NH_2 + 2H_2O.$$

Secondary amines of the aromatic series may be obtained from the acetyl derivatives of the primary. Thus aniline heated with acetic acid gives acetanilide,

$$C_6H_5NH\boxed{H} + CH_3CO\boxed{OH} = H_2O + C_6H_5NH(COCH_3),$$

and when this substance is acted upon by sodium in an indifferent solvent, such as toluene, the corresponding sodium derivative is obtained,

$$C_6H_5NH(COCH_3) + Na = H + C_6H_5N\langle^{Na}_{COCH_3}.$$

This readily reacts with an aliphatic halogen derivative giving the corresponding alkyl-acetanilide, which on treatment with potash is broken down into the secondary amine and acetic acid,

i. $C_6H_5N\langle^{Na}_{COCH_3} + C_2H_5I = NaI + C_6H_5N\langle^{C_2H_5}_{COCH_3}$

ii. $C_6H_5N\langle^{C_2H_5}_{COCH_3} + KOH = \underset{\text{Ethyl aniline.}}{C_6H_5NHC_2H_5} + CH_3COOK$

4. Acid amides of the aliphatic series on treatment with bromine or potash give amines containing one less carbon atom. The first phase of the reaction consists in the formation of bromamides,

$$CH_3CONH_2 + Br_2 + KOH = CH_3CONHBr + KBr + H_2O$$

These derivatives are then further broken down into amines,

$$CH_3CONHBr + 3KOH = KBr + K_2CO_3 + \underset{\text{Methylamine.}}{CH_3NH_2}$$

This method is applicable to the amides of the fatty series up to those containing five carbon atoms.

In the aromatic series this reaction is used for the commercial production of anthranilic acid, and has been one of the chief factors in the success of the indigo synthesis.

i. $C_6H_4\langle^{CO}_{CO}\rangle NH + KOH = \underset{\text{Mon-amide of phthalic acid.}}{C_6H_4\langle^{CONH_2}_{COOK.}}$

ii. $C_6H_4\langle^{CONH_2}_{COOK} + Br_2 + KOH = C_6H_4\langle^{CONHBr}_{COOK} + KBr + H_2O$

iii. $C_6H_4\langle^{CONHBr}_{COOK} + 3KOH = \underset{\text{Anthranilic acid.}}{C_6H_4\langle^{NH_2}_{COOK}} + K_2CO_3 + KBr + H_2O$

General Properties of the Ammonia Derivatives.

The lower members of the **aliphatic amines** are gases with ammoniacal odour, and are readily soluble in water; the higher members are liquids also soluble, and it is only in the case of those with high molecular magnitude that the solubility in this liquid becomes slight. They are stronger bases than ammonia, the basicity increasing in proportion to the number of alkyl groups replacing hydrogen atoms of the original ammonia.

On the other hand, in the case of aromatic amines, this property is powerfully depressed, aniline is a weak base; diphenylamine, $(C_6H_5)_2NH$, still weaker; and in triphenylamine, $(C_6H_5)_3N$, this characteristic has entirely disappeared. The entrance of halogen atoms or nitro groups into the nucleus of aniline further depresses its already slight basic properties.

The aromatic amines are colourless liquids or solids, having a peculiar and characteristic smell; unlike the aliphatic they have no alkaline reaction, and are only slightly soluble in water.

The reactivity of primary and secondary amines of both series, as compared with the tertiary, is dependent on the ease with which the hydrogen atoms of the original ammonia are replaced. In the aromatic series, unlike the aliphatic, the hydrogen atoms in the primary and secondary amines may be replaced by potassium.

Primary and Secondary Amines of both series behave in a characteristic manner with nitrous acid. Primary amines of the fatty series yield alcohols,

$$C_2H_5NH_2 + HNO_2 = C_2H_5OH + H_2O + N_2.$$

In the aromatic series, the important di-azo reaction takes place (see p. 41).

The Secondary Amines of both series give nitrosamines,

i. $$(C_2H_5)_2NH + HNO_2 = H_2O + (C_2H_5)_2NO$$

Diethyl-nitrosamine.

ii. $$C_6H_5NH.CH_3 + HNO_2 = H_2O + C_6H_5N\langle^{NO}_{CH_3}$$

Nitrosamine of methyl aniline.

The nitrosamines of the aromatic series undergo an interesting intramolecular change, on treating their alcoholic solution with hydrochloric acid, when *p*-nitroso derivatives are obtained.

$$C_6H_5N\langle^{NO}_{CH_3} \rightarrow NO.C_6H_4.NHCH_3.$$

p-nitroso-methyl aniline.

The Tertiary Amines of the Aliphatic Series either do not react at all with nitrous acid, or are completely decomposed; whereas in the aromatic series, the hydrogen atom in the 1 : 4 position in the ring is attacked, with the formation of *p*-nitroso derivatives.

$$(CH_3)_2N.C_6H_5 + HNO_2 = (CH_3)_2N.C_6H_4.NO + H_2O.$$

p-nitroso-dimethyl aniline.

The aliphatic amines are of little if any physiological importance, and in consequence the following statements and reactions will only apply to the amines of the aromatic series.

Both aniline and *p*-amido phenol,

$$C_6H_4\begin{matrix}OH\\NH_2\end{matrix}$$

are very sensitive to oxidizing agents, but their stability can be very largely increased by their conversion into a group of derivatives called the **Anilides.** These may be obtained by the action of the acid, or acid chloride or anhydride, on the amine (see p. 120).

$$C_6H_5NH\boxed{H} + CH_3CO\boxed{OH} = C_6H_5NH.COCH_3 + H_2O$$

Acetanilide.

$$C_6H_5NH\boxed{H} + CH_3CO\boxed{Cl} = C_6H_5NH.COCH_3 + HCl$$

or $$C_6H_5NH\boxed{H} + C_6H_5CO\boxed{Cl} = C_6H_5NH.COC_6H_5 + HCl$$

Benzanilide.

It is possible by this means to introduce a variety of different radicals in place of the hydrogen of either primary or secondary amines.

The acid anilides are very stable derivatives, they can often be distilled without change, and also directly nitrated or sulphonated. They are characterized by their great power of crystallization, and consequently serve as a means of detecting many of the aromatic bases.

The introduction of the acidic grouping, as might be expected, depresses the basic characteristics, methyl acetamide, $CH_3NH.COCH_3$, is only slightly basic, the hydrochloride of acetanilide is decomposed by water. Modified characteristics similar to this are observed on the entrance of acidic groupings into basic substances. Thus the powerful base methylamine, CH_3NH_2, becomes glycocol, $COOH.CH_2.NH_2$, on the replacement of hydrogen by the acidic COOH group; in this substance both the basic properties of the NH_2 group and the characteristics of the COOH are very consider-

ably modified. Phenol, C_6H_5OH, has powerful acidic properties, and forms salts by the replacement of the hydroxyl hydrogen atom; *p*-amido phenol,

$$C_6H_4\begin{matrix}OH\\NH_2,\end{matrix}$$

by the entrance of the NH_2 group, has entirely lost this salt-forming power, the already slight basic properties of aniline being still further depressed.

The anilides are broken down into their components on treatment with alkalis or heating with mineral acids, and the physiological reaction of these derivatives is due to this decomposition taking place in the organism.

General Physiological Properties.

The physiological effect following the entrance of the ammonia residue is dependent, firstly and chiefly, on the nature of the nucleus into which it enters, and secondly on the reactivity of the nitrogen complex; thirdly a curious variation of physiological reactivity is noticed when trivalent derivatives pass over into those of the ammonium type.

Ammonia itself, and its salts, are remarkable in differing from the caustic alkalis, which are in combination depressant, whereas ammonia is a stimulant.

Intravenously injected, ammonia produces tetanic convulsions, partly cerebral and partly spinal in origin; the convulsions are not so markedly reflex in character as those produced by strychnine. The irritability of the spinal reflexes is, however, increased. It also quickens the heart and respiration: the latter action is probably due to stimulation of the centre in the medulla. The rise of blood pressure, which almost immediately follows the preliminary fall, is not due to central action, but appears to be partly, at least, a consequence of the increased cardiac action. The main difference between the action of ammonia and strychnine is due to the rapid paralysis of the motor nerve endings by the former, which prevents the supervention of tetanus.

When the hydrogen atoms are replaced by radicals of the aliphatic hydrocarbons these characteristics disappear, and the resulting primary, secondary, and tertiary amines irritate the mucous membrane, but otherwise have slight, if any, physiological reaction. Further, the replacement of two hydrogen atoms by amido groups, e. g. in tetramethylene diamine, $NH_2(CH_2)_4NH_2$, or penta-

methylene diamine, $NH_2 . CH_2 . (CH_2)_4 . NH_2$, gives rise to similarly inactive substances.

When the amido group replaces hydroxyl in the aliphatic acids, resulting in the formation of bodies of the nature of acetamide, CH_3CONH_2, it is again found that pharmacologically inactive bodies result. If the amido group replaces hydrogen in the aliphatic nucleus of these acids, the result is similar. $NH_2 . CH_2 . COOH$, amido acetic, $NH_2 . CH_2 . CH_2 . COOH$, β-amido propionic acids, &c., are inert, but unlike acetamide these are broken down in the organism, as previously described (p. 74).

Betaine, trimethylglycocol, $CH_2(N(CH_3)_3) . COO$,

is physiologically inactive, and its hydrochloride, under the name of **Acidol,** has been introduced as a solid substitute for hydrochloric acid; it is very readily soluble in water, and contains 23·78 per cent. acid, which is slowly split off in the stomach.

When the amido group replaces a hydrogen atom in the benzene nucleus, substances of the nature of aniline result, and a completely new and valuable set of pharmacological properties appear; this observation has formed the basis for the synthesis of a large group of so-called 'antipyretics', which will be described later.

The entrance of a second amido group into the aromatic nucleus gives rise to powerfully toxic substances unlike the corresponding aliphatic diamines.

The passage of a primary aromatic amine to a secondary is followed by a corresponding alteration in physiological properties. Methyl, ethyl, and amyl aniline are less toxic than aniline, and have lost the power which that substance possesses of producing muscular spasms, but, on the other hand, they bring about the paralysis of the peripheral endings of the motor nerves, in a somewhat similar manner to the alkyl alkaloids, although without the curare action of the quinquevalent nitrogen derivatives. (Compare action of antifebrin and exalgin.)

The presence of an imido group may result in an increase of toxicity, most probably due to increase of reactivity. Thus, guanidin

$$NH.C\begin{matrix}NH_2\\NH_2\end{matrix}$$

is a powerful poison. Xanthine, with three imido groups, is, according to Filehne, more toxic than theobromine with one, and this more

toxic than caffeine, in which all the imido hydrogen atoms have been replaced by methyl groups. Piperidine is much more toxic than pyridine.

The Quaternary Ammonium Compounds show a most striking difference from those of the trivalent type, and to a very large extent their physiological reaction is independent of their chemical composition. All the following substances produce paralysis of the peripheral endings of the motor nerves:—ammonium iodide, ethyl ammonium chloride, trimethyl ammonium iodide, tetraethyl ammonium iodide; aromatic derivatives, such as phenyl-dimethyl-ethyl ammonium iodide, phenyl-triethyl ammonium iodide. Also various alkyl alkaloids in which nitrogen is in the quinquevalent condition, such as methyl strychnine, methyl quinine, methyl morphine, ethyl brucine, ethyl nicotine,[1] curare. And what is still more striking, this curare-like action is to be observed in the corresponding quinquevalent arsenic, antimony, and phosphorus bases, substances which may be regarded as ammonium salts in which nitrogen has been replaced by these elements (see also p. 53).

Alteration in the Physiological Action of Bases by replacement of (A) Hydrogen of Amido Group by Acid Radicals.

The introduction of both aliphatic and aromatic acid radicals, by methods already mentioned, is followed by a drop in toxicity, depending entirely upon the greater stability of the resulting compounds, which are but slowly decomposed by the organism.

As a rule, the replacement of both hydrogen atoms of the amido group by such radicals of the aliphatic series, gives rise to substances which are so readily decomposed, even by water, into the mon-acid derivatives, that these possess no advantages over the former group.

The acetyl radical is that most usually introduced, and other radicals of the aliphatic series do not possess any great advantage over this, with the possible exception of the lactyl, whose derivatives are usually more soluble in water. The replacement of hydrogen by radicals of the aromatic acids, such as benzoic or salicylic, gives rise to substances which are usually very insoluble, and offer

[1] The ammonium compounds of the alkaloids will be further dealt with when those bodies are considered in detail. It must be remembered, however, that for practical purposes, the result of converting the nitrogen from a trivalent to a quinquevalent condition may merely be to diminish but not otherwise to alter the physiological action of the alkaloid as far as its purely therapeutic action is considered.

great resistance to decomposition in the organism, with the result that they are usually completely, or almost completely, inactive physiologically. But it must be remembered that whereas the aliphatic radicals, with exception of perhaps lactic and citric acids, have no pharmacological action, some of the aromatic acids have a considerable effect, such, for instance, as salicylic (p. 151).

Consequently, if such an acid is one of the decomposition products of the acyl-nitrogen derivative, its action will appear together with that of the basic residue.

B. Hydrogen of Hydroxyl Group by Acid Radicals.

Whereas the replacement of hydrogen of the amido group by acid radicals brings about a decrease in toxicity, a different action is noticed when the hydrogen of an hydroxyl group is similarly displaced. In this case an increase in toxic properties is noticed. Ecgonine methyl ester, $C_{10}H_{16}NO_2.OH$, has no local anaesthetic action; by the replacement of the hydroxyl hydrogen by benzoyl, cocaine results, $C_{10}H_{16}NO_2.O.COC_6H_5$, a powerful local anaesthetic.

Benzoyl lupinine is much more toxic than lupinine.

$C_{10}H_{18}N.O.CO.C_6H_5$	$C_{10}H_{18}N.OH$
Benzoyl-lupinine.	Lupinine.

Mono-acetyl morphine, diacetyl morphine (**Heroine**), benzoyl morphine, and dibenzoyl morphine have a similar physiological action to codeine (methyl morphine), but are far more toxic. The depressant effect on the spinal cord, and especially on the respiratory centre, is much greater than that of morphine. Compared with codeine, one-tenth of the dose will produce a similar narcotic effect.

Veratrine may be split up by the action of an alkali into cevine and tiglinic acid,

$$\underset{\text{Veratrine.}}{C_{32}H_{49}NO_9} + H_2O = \underset{\text{Tiglinic acid.}}{C_5H_8O_2} + \underset{\text{Cevine.}}{C_{27}H_{43}NO_8}$$

Cevine has the same physiological action as veratrine, but its toxicity, owing to the absence of the substituted acid group, is ten times less.

The increase in toxicity produced by the introduction of the acid group does not depend on the physiological action of that group in itself, but upon its power of covering certain 'anchoring' groups in the molecule, so that the latter, being more generally resistant, can produce a specific action (i.e. on the central or peripheral nervous

system). The acid radical may also form an anchoring group itself for the production of a special physiological response.

ANILINE DERIVATIVES.

The discovery of Cahn and Hepp that aniline (or acetanilide) is a powerful antipyretic, and also possesses antineuralgic properties, together with the low price of this substance, has led to the production of a large number of its derivatives.

Aniline and its salts have a powerful antipyretic action, like phenol, and it produces spasmodic muscular contractions of central origin, as does ammonia. The main toxic symptoms are weakness, dizziness, cyanosis, and finally collapse, with or without vomiting due to direct irritation of the gastric mucosa.

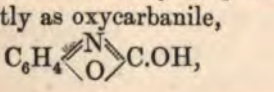
Aniline also breaks up the red blood cells, liberating the haemoglobin.

Toxic symptoms of a similar nature but less pronounced character are observed among workers in the dyeing industry, in which aniline oil is used.[1] Aniline was at one time employed as a remedy for phthisis and other forms of tuberculous disease, the vapour being inhaled in combination with certain aromatic antiseptics. Like most schemes for internal antisepsis, however, this failed when put to a practical test; the tubercle bacilli in the blood-stream remained unaffected, whereas the patients exhibited symptoms of poisoning due to the presence of the drug.

It was only to be expected that when the reactive amido group is rendered more stable by replacing hydrogen with the acetyl group, the resulting acetanilide (antifebrin) should be a far less toxic substance.

Antifebrin, $C_6H_5NH(COCH_3)$, shows the same general reaction as aniline. It reduces fever, has similar antineuralgic properties, and a similar though less marked action on the red blood corpuscles; but the effect, dependent as it is on the decomposition of the anilide in the organism, is not produced so rapidly as by the free base. No effect on nitrogenous metabolism occurs with therapeutic doses. In pyrexia a slight diminution may occur.

Acetanilide is oxidized in the body to *p*-aminophenol and is excreted in the urine partly as oxycarbanile,



[1] Dearden, British Medical Association Meeting, 1902.

p-acetyl-aminophenol, and *p*-aminophenol. The latter is further changed by combination with sulphuric and glycuronic acids. These changes in structure diminish the toxicity of aniline or acetanilide, but do not destroy entirely their antipyretic action.

The most varied acid radicals have been introduced in place of the acetyl group in acetanilide, but without the production of substances with any novel physiological reaction; since this factor is unquestionably a function of the decomposition of these derivatives into aniline, this was hardly to be expected. It is only when the entering group has physiological characteristics of its own that these may appear simultaneously with those of aniline.

Among substances of this type are the following:—

1. Formanilide, $C_6H_5NH(OCH)$, formed by rapidly heating oxalic acid and aniline, or treating aniline with formic acid. It has powerful antipyretic and analgesic properties, and acts as a local anaesthetic, but is much more toxic than acetanilide, this being undoubtedly due to the fact that it is much more easily decomposed by dilute acids.

2. Benzanilide, $C_6H_5NH(COC_6H_5)$, is only broken down by the organism with difficulty, and consequently larger doses are required than in the case of acetanilide.

3. Salicylanilide, $C_6H_5NH(COC_6H_4.OH)$, and anisanilide, $C_6H_5NH(COC_6H_4.OCH_3)$, like most derivatives of this type, are only broken down by the organism with such difficulty that their physiological reaction is but slight.

Attempts to increase the solubility of acetanilide by the formation of such substances as acetanilidoacetic acid and formanilidoacetic acid, by the action of chloracetic acid on acetanilide or formanilide,

$$C_6H_4N\langle{}^{H}_{R} + Cl.CH_2.COOH = HCl + C_6H_4N\langle{}^{CH_2.COOH}_{R},$$

when R = $(COCH_3)'$ or $(CHO)'$, gave negative results, since these substances, having lost their basic characteristics and become acids, obey the general rule that such derivatives thereby lose their physiological properties. Formanilidoacetic acid, however, owing to its instability, is about as toxic as formanilide. For similar reasons,

Cosparin,

$$C_6H_4\langle{}^{NHCOCH_3}_{SO_2ONa}$$

the *p*-sulphonate of acetanilide, obtained by the action of acetic acid

on sulphanilic acid,

$$C_6H_4\begin{matrix}SO_2OH\\NH_2\end{matrix}\ 1:4,$$

should have no physiological importance, since its action can only depend on its decomposition into the inert sulphanilic acid.

In order to increase the solubility of acetanilide and phenacetin, derivatives were obtained containing the sulphonic group in place of the hydrogen of the methane radical; these were prepared firstly by dehydrating the aniline salt of monochloracetic acid by means of phosphorus pentoxide,

$$CH_2Cl.COO(C_6H_5NH_3) - H_2O = CH_2Cl.CO.NHC_6H_5,$$

and then heating this latter substance in aqueous solution with sodium sulphite—

$$C_6H_5NH.(COCH_2Cl) + Na_2SO_3 = NaCl + C_6H_5NH.(CO.CH_2.SO_2ONa)$$

The resulting substances are much more soluble than acetanilide or phenacetin, and, if their action is similar, which is stated to be the case, they must be broken down in the organism, the acidic grouping not being sufficiently stable for them to obey the general rule.

Another method of modifying the action of aniline, that is of making it more stable, consists in converting it into a urethane derivative by the action of chlorformic ester—

$$C_6H_5NH\!:\!H + Cl\!:\!COOC_2H_5 = HCl + C_6H_5NH.COOC_2H_5$$

Phenyl urethane.

The resulting substance, termed **Euphorin,** is much less toxic than aniline. Physiologically its action resembles that of acetanilide rather than that of urethane. It depresses the temperature, and has considerable analgesic properties. Large doses weaken the pulse and respiration. It has also a bactericidal action, and has been employed to check suppuration. It is not of value as a hypnotic like other urethane derivatives (hedonal, &c.). It does not lead to the formation of methaemoglobin. In large doses it acts like a urethane derivative, paralysing the central nervous system; the effect is very similar to the paretic action of alcohol. In moderate doses it is said to decrease metabolic processes, but its antipyretic action is similar to that of the other bodies of this group, being due to the dilatation of the cutaneous vessels. It increases the conjugated sulphates in the urine, and is partly excreted as oxyphenyl urethane, an indication consequently that this derivative is less toxic than euphorin itself (see p. 196).

Whereas Exalgin (methylacetanilide) has powerfully toxic properties, the corresponding **Methyleuphorin,**

$$C_6H_5 . N\begin{matrix}CH_3\\COOC_2H_5,\end{matrix}$$

is an almost indifferent substance.

When aniline is converted into the secondary amine, methyl-aniline, $C_6H_5NHCH_3$, a substance is obtained which paralyses the motor nerve endings. **Exalgin**, which is the acetyl derivative of this,

$$C_6H_5 . N\begin{matrix}CH_3\\COCH_3,\end{matrix}$$

has a somewhat similar action to acetanilide, but a powerfully toxic secondary reaction, producing epileptic convulsions and profuse salivation. Death results from respiratory failure. The convulsions can be stopped by the induction of anaesthesia, and are probably partly cerebral and partly spinal. Smaller (non-toxic) doses produce in mammals lethargy and a fall of arterial pressure.

Finally, the replacement of aniline by any of the toluidines has no advantages, since they act on the red blood corpuscles, forming methaemoglobin in a similar manner to aniline itself.

On injection into the jugular vein of a dog the lethal dose of these bases per kilo. weight has been found to be: *ortho*-toluidine ·208 gm., 1 : 3-toluidine ·125 gm., 1 : 4-toluidine ·1 gm.

But when converted into their acetyl derivatives a considerable difference is noticed; both 1 : 3 and 1 : 4 are non-toxic, and this characteristic is only noticed with the 1 : 2 substance. Then it is only the 1 : 3 derivative that has antipyretic properties, and Barbarini states that it is less toxic and has a stronger action than antifebrin.

Aniline and *m*-toluidine depress the respiratory capacity more than either the *o*- or *p*-derivative; further, the former substances depress the temperature to a greater extent than the latter.

DERIVATIVES OF *p*-AMIDO-PHENOL, $C_6H_4\begin{matrix}OH\\NH_2\end{matrix}$ 1 : 4.[1]

On their passage through the organism, aniline, acetanilide, or generally speaking, any of the physiologically active derivatives of

[1] 1 : 2-amido phenol, unlike the 1 : 4 derivative, is inactive, but when the hydroxyl hydrogen atom is replaced by alkyl radicals, bodies possessing narcotic properties result; the 1 : 2 and 1 : 3 present no pharmacological advantage, and are both more toxic than the *para* derivative.

these substances, are partially converted in *p*-amido-phenol, which is eliminated as a sulphonate or as a compound of glycuronic acid. Since observations have shown that such changes always tend to the production of less toxic derivatives, it was but natural to investigate the therapeutic value of this substituted aniline. The chemical nature of this substance, and the modifications of the characteristics of each substituent by their simultaneous presence in the molecule, have already been described: the pharmacological properties are those to be expected, viz. energetic antipyretic action, but much less toxicity and haemolytic action than is shown by aniline. The whole group of physiologically active derivatives of aniline or *p*-amido-phenol are broken down in the organism with the production of this latter substance, and the indophenol reaction in the urine may be taken as a test for their reactivity.

Trenpel and Hinsberg have stated that the 'antipyretic action of aniline and *p*-amido-phenol derivatives appears to be, within certain limits, proportional or nearly proportional to the amount of aniline or *p*-amido-phenol or phenetidin formed in the organism'. On the other hand, if these substances are not formed (i. e. if no indophenol reaction with the urine occurs), then the preparation is not physiologically active.

Thus,

Methacetin, $C_6H_4\begin{matrix}OCH_3\\NH.COCH_3\end{matrix}$, Phenacetin, $C_6H_4\begin{matrix}OC_2H_5\\NH.COCH_3\end{matrix}$,

and acetamidophenol-propyl-ether, $C_6H_4\begin{matrix}OC_3H_7\\NH.COCH_3\end{matrix}$,

are readily decomposed in the organism, giving *p*-amido-phenol, and show physiological characteristics similar to those derivatives of phenacetin,

$$C_6H_4\begin{matrix}OC_2H_5\\N\begin{matrix}R\\COCH_3\end{matrix}\end{matrix},$$

in which R = CH_3, C_2H_5, C_3H_7, or *iso*-propyl groups. But ethyl-acetamido phenol,

$$C_6H_4\begin{matrix}OH\\N\begin{matrix}C_2H_5\\COCH_3\end{matrix}\end{matrix},$$

which is not decomposed, has no antipyretic or other action.

It will be readily seen that the general physiological reaction of the whole of the *p*-amido-phenol derivatives will be that of the free base itself, or of its ethoxy or methoxy substitution product.

added to this reaction will be that of the radical attached to the amido group; in the case of acid derivatives of the aliphatic series, for example, this would be nil.

In the case of *p*-amido-phenol, two different classes of modifications can be carried out; either the hydrogen of the hydroxyl group can be replaced by radicals, or the hydrogen atoms of the amido group can be similarly displaced.

The replacement of H in the NH_2 group by acetyl, giving acetamido-phenol,

$$C_6H_4\begin{matrix}OH\\NHCOCH_3,\end{matrix}$$

results in the production of a substance with powerful antipyretic, antineuralgic, and possibly slight narcotic properties, but of much lower toxicity than the original substance. The further replacement of the hydrogen of the hydroxyl group by methyl,

$$C_6H_4\begin{matrix}OCH_3\\NHCOCH_3\end{matrix}$$

(methacetin), causes an increase in both the former properties and a decrease in the action on the blood; replaced by ethyl,

$$C_6H_4\begin{matrix}OC_2H_5\\NHCOCH_3\end{matrix}$$

(phenacetin), the narcotic action is increased, and a further diminution in the formation of methaemoglobin is noticed. The maximum antipyretic and antineuralgic action is found in the case of methyl, but lesser toxicity in case of ethyl. The antipyretic action diminishes with the increasing molecular magnitude of the group replacing H of the hydroxyl. In one direction, then, the possible variations as regards alkyl groups replacing that hydrogen atom is limited to either methyl or ethyl.

In phenacetin the hydrogen atom R,

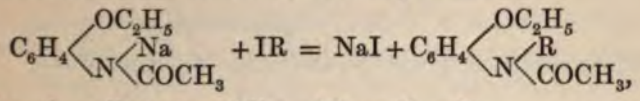
$$C_6H_4\begin{matrix}OC_2H_5\\N\begin{matrix}R\\COCH_3,\end{matrix}\end{matrix}$$

may be replaced by acid groups, which will be discussed later, or by radicals of the aliphatic hydrocarbons. The entrance of methyl causes an increase in the narcotic and also in the antineuralgic properties, but the substance has only a slight antipyretic power.

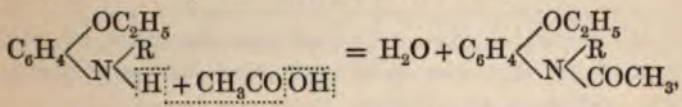
Replaced by ethyl, a similar decrease in toxicity, increase in narcotic, and decrease in antipyretic properties are noticed.

As the molecular magnitude of the entering group increases, i. e. in *n*-propyl and *iso*-propyl, *n*-butyl and *n*-amyl, the narcotic property rapidly diminishes. In this group the maximum narcotic and anti-neuralgic action is found when the entering group is methyl, the maximum antipyretic when the groups are either methyl or ethyl, the minimum toxicity in the case of ethyl.

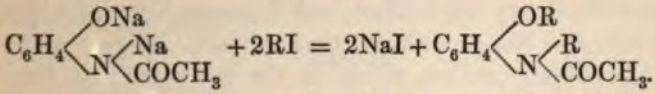
Substances of the above type can be prepared by the action of alkyl iodides on the sodium derivative of phenacetin,



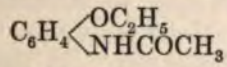
or by treating alkyl phenetidins with acetic acid,



or by converting *p*-acetylamido phenol into its di-sodium derivative and then acting upon this with alkyl iodides—



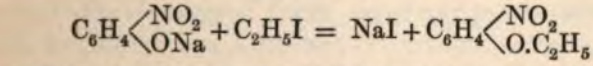
The best-known member of the whole group is **Phenacetin,**



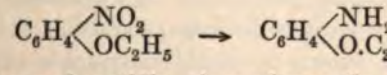
This substance may be obtained from phenol by the following reactions :—

1. On nitration, phenol gives rise to a mixture of *o*- and *p*-nitro-phenol, of which the former may be removed by distillation with steam.

2. *p*-Nitro-phenol is converted into its sodium salt, and this on treatment with ethyl iodide gives *p*-nitro-phenetol—



3. *p*-Nitro-phenetol is reduced to the amido derivative by means of tin and hydrochloric acid,



The resulting *p*-phenetidin gives phenacetin on treatment with glacial acetic acid.

As the preparation of *p*-nitro phenol in a state of purity is by no means easy; the method of preparation is modified. *p*-Phenetidin is diazotized and treated with a phenol and sodium carbonate,

$$C_6H_4\begin{matrix}OC_2H_5\\NH_2\end{matrix} \rightarrow C_6H_4\begin{matrix}OC_2H_5\\N:N.OH\end{matrix} \rightarrow C_6H_4\begin{matrix}OC_2H_5\\N:N.C_6H_4.OH\end{matrix}$$

and the resulting compound is readily converted into the di-ethoxy derivative

$$C_6H_4\begin{matrix}OC_2H_5\\N:N.C_6H_4.OC_2H_5,\end{matrix}$$

which, on reduction, gives two molecules of phenetidin—

$$C_6H_4\begin{matrix}OC_2H_5\\NH_2\end{matrix}$$

Half of the yield is then converted into phenacetin by means of acetic acid, and the other half again used for the preparation of a fresh quantity of phenetidin.

Physiologically the toxic effect of this substance is not great. Dujardin Beaumetz gave 2·5 grams to a rabbit weighing 2·26 kilograms without any toxic effect, and 2 grams have been given for every kilogram body-weight in other animals. Large doses produce the characteristic aniline action on the red corpuscles, the blood becomes thick and purple, and finally shows the spectrum of methaemoglobin. The darkening of the urine also takes place, and occasionally a reducing substance appears. The 'antipyretic action' is thus explained by Schmiedeberg. In the first place, metabolism experiments have shown that the nitrogen excretion is increased with small doses, and only decreased with large ones; thus a direct decrease in nitrogenous metabolism cannot be the cause of the fall in temperature. Now, if animals in which the temperature has been raised by puncture of the corpus striatum are given moderate doses of phenacetin or one of its congeners, or even small doses of morphine (·01–02 grams, $\frac{1}{6}$–$\frac{1}{3}$ grain), a fall of temperature is observed after one or two hours, which, however, is only temporary. If this experiment, however, is performed, and the animal placed in an incubator at 31–32° C., no fall of temperature takes place; thus, the fall of temperature must be induced by increased heat-loss, and not by diminished heat production. Large doses of these drugs, however, paralyse the centre for heat production.

The heat-loss is shown by plethysmographic experiments to be due to dilatation of the cutaneous vessels, with a corresponding contraction of the internal arterioles.

The characteristic analgesic action of phenacetin is mainly due to its effect on the sensory tracts in the cord.

Phenacetin is, however, only slightly soluble in water, and consequently is only slowly absorbed. Many attempts have been made to increase the solubility without so diminishing the stability of the substance as to cause its decomposition or rapid decomposition by a 2 per cent. solution of hydrochloric acid, whereby the toxic hydrochloride of phenetidin would be formed in the stomach. For this purpose various acid radicals have been introduced into the basic NH_2 group, and the following examples, which are classified according to the type of chemical modification, show that (1) only in some cases has the desired result followed; (2) the substances described illustrate the modifications in the physiological reaction which can be obtained by such variations of the molecular structure; (3) no substance has been obtained, by such modifications, with any novel pharmacological properties, nor of course was this likely, if the action of these derivatives actually depends, as it most probably does, on their decomposition into one and the same substance, *p*-amido-phenol or its ethyl ether.

Class I.

1. Formyl-phenetidin,

$$C_6H_4\begin{matrix}OC_2H_5\\NH(COH)\end{matrix}$$

formed by acting with formic acid and sodium formate on phenetidin, has an action entirely different from that of the other derivatives of this substance. The antipyretic effect almost entirely disappears, and is replaced by a powerfully depressant action on the cells of the spinal cord. It is, in fact, a physiological antagonist to strychnine, but unfortunately it has no therapeutic value in checking convulsions caused by disease.

2. Propyl-phenetidin,

$$C_6H_4\begin{matrix}OC_2H_5\\NH.(COCH_2.CH_3)\end{matrix}$$

termed **Triphenin** by Mering, has similar properties to phenacetin, but its slight solubility results in slow absorption, and consequent mild physiological reactivity.

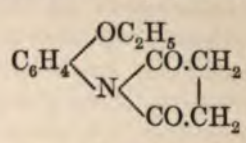
3. Lactyl-phenetidin,

$$C_6H_4\begin{matrix}OC_2H_5\\NH(CO.CH.OH.CH_3)\end{matrix}$$

(**Lactophenin**), is obtained by heating the lactic acid salt of the

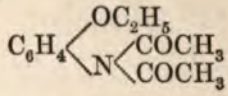
base to 130°–180°, or by heating lactic anhydride or lactic ester with the base to this temperature; or it may be obtained by replacing the halogen in α-brompropionyl-phenetidin by OH, through the agency of aqueous sodium acetate. Its action appears to be identical with that of phenacetin, but it is more soluble; the narcotic action is well marked, though the antipyretic action is slighter. It is mainly valuable as an antineuralgic. In rabbits its effect closely resembles that produced by chloral hydrate, the animal remaining unconscious and motionless, and irresponsive to painful reflexes, though the respiration and circulation are not affected (Schmiedeberg). It is more liable than phenacetin to lead to the formation of the toxic hydrochloride of phenetidin in the stomach.

4. *p*-Ethoxyphenyl-succinimide (**Pyrantin**)



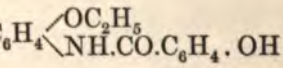
is obtained by the action of succinic anhydride on the base. The sodium salt is soluble in water. It is an uncertain antipyretic and analgesic, but is said to have no toxic action on haemoglobin.

5. Diacet-phenetidin



was thought likely, on theoretical grounds, to prove a more powerful antipyretic than phenacetin, but in actual practice this was not established. It is very unstable.

6. Salicyl-phenetidin



(**Salophen** or **Saliphenin**), like the majority of such derivatives, is only broken down in the organism with difficulty. It was originally introduced to replace salol, in order to avoid the formation of phenol in the organism. It is unaffected by the gastric juice, but decomposed by the pancreatic. It is slightly antipyretic, but appears mainly active as to the salicyl portion of the molecule. It is mostly excreted unchanged in the urine. No increase in the conjugated sulphates occurs. Quinic acid produces a similarly inert compound with phenetidin.

7. **Amygdophenin,**

$$C_6H_4\begin{cases}OC_2H_5\\NHCO.CH(OH).C_6H_5,\end{cases}$$

is obtained by heating *para*-phenetidin with mandelic acid at 130°–170° C. The mandelic acid diminishes the toxicity and the antipyretic action by diminishing the solubility and rapidity of absorption.

Class II.

A. Attempts to increase the solubility of phenacetin by the ordinary methods employed in organic chemistry, that is by the introduction of a (COOH) or (SO_2OH) group into the nucleus, were unlikely to lead to the desired result, since Nencki had shown that such changes tend to destroy physiological activity. Thus, both the soluble phenacetin sulphonic acid,

$$C_6H_3\begin{cases}OC_2H_5\\NH.COCH_3\\SO_2OH\end{cases}$$

and phenacetin carboxylic acid,

$$C_6H_3\begin{cases}OC_2H_5\\NH.COCH_3\\COOH\end{cases}$$

prepared in Schering's laboratory, are but very slightly reactive.

Phesin, the sodium salt of the former acid,

$$C_6H_3\begin{cases}OC_2H_5\\NHCOCH_3\\SO_2ONa\end{cases}$$

is a light-brown powder, soluble in water, with a slightly astringent salt taste. It is employed in doses of 15–30 grains, and apparently possesses analgesic and antipyretic action.

On the other hand, the introduction of a second amido group into the nucleus, affording another possibility for the preparation of soluble derivatives, is not feasible, since it results in a large increase in toxicity.

B. The replacement of hydrogen in the amido group by acid radicals has led to the preparation of several substances of greater solubility than phenacetin. But it was hardly to be expected that, if the stability of the body were such as to allow of its decomposition, giving *p*-amido-phenol in the organism, there should be any

considerable decrease in toxicity; if, on the other hand, the stability was great, then the presence of acid groups might be expected to give rise to substances with little if any physiological activity.

1. The citric acid derivatives of phenetidin are:—

i. CH_2COOH
$C.OH.COOH$
$CH_2 . CO-NH.C_6H_4 . OC_2H_5$ **Apolysin,**

ii. $CH_2 . CO.NH.C_6H_4 . OC_2H_5$
$C.OH.COOH$
$CH_2 . CO.NH.C_6H_4 . OC_2H_5$.

Apolysin is soluble in about 80 parts of cold water, and freely in hot water, alcohol, and glycerin. It has been used in migraine, but is said by some observers to have neither the analgesic nor the antipyretic properties of phenacetin. It is, like lactophenin, easily decomposed by the hydrochloric acid in the stomach, giving rise to the toxic phenetidin salt; this produces both local and general symptoms. If injected subcutaneously no decomposition occurs, and the substance passes unchanged into the urine; its only physiological action then is due to the acid radicals.

Citrophen (Citrophenin), $CH_2 . CO.NH.C_6H_4OC_2H_5$
$C.OH.CO.NH.C_6H_4OC_2H_5$
$CH_2 . CO.NH.C_6H_4 . OC_2H_5$

is soluble in 40 parts of water, and has a pleasant taste. Its action resembles that of phenacetin. The formula given above was that given by Roos; Hildebrand, however, states that it is merely the citrate of phenetidin; its action physiologically is similar to that of a salt of phenetidin, and not to that of a true substitution product. Chemically it gives a red coloration with perchloride of iron, which apolysin does not. It is a blood poison like the other phenetidin salts.

2. Schmidt prepared ethoxy-succinanilic acid,

$$C_6H_4\begin{matrix}OC_2H_5\\ NH.CO.CH_2 . CH_2 . CO.OH,\end{matrix}$$

and ethoxytartranilic acid,

$$C_6H_4\begin{cases}OC_2H_5\\NH.CO.CHOH.CH.OH.COOH,\end{cases}$$

but owing to the introduction of the acid group, these bodies have no antipyretic action.

3. In a similar manner ethoxyphenyl-glycin,

$$C_6H_5\begin{cases}OC_2H_5\\NH.CO.CH_2.COOH,\end{cases}$$

has been found to possess no pharmacological value.

4. **Phenosal,**

$$C_6H_4\begin{cases}OC_2H_5\\NH.CO.CH_2.O.C_6H_4.COOH,\end{cases}$$

obtained by heating salicylacetic acid with phenetidin to 120°, is a white crystalline powder, soluble with difficulty in water, alcohol, and ether. It has a bitter acrid taste, and has been employed for its antipyretic and analgesic qualities, which, however, are but slight.

Class III.

Schmidt and Majert, in order to increase the solubility of phenacetin, prepared amido-phenacetin (glycocoll,-phenetidin, **Phenocoll**),

$$C_6H_4\begin{cases}OC_2H_5\\NH.CO.CH_2NH_2\end{cases}$$

by the action of ammonia on bromacetyl phenetidin. The hydrochloride is soluble in 16 parts of water, forming a solution of bitter, saline taste. It has the usual phenacetin-like action, and a few authors state that it is an antiperiodic. This is not, however, generally accepted. It appears to have some antiseptic properties, as it has been employed externally as a substitute for iodoform.

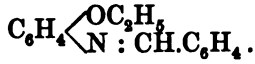
Phenocoll hydrochloride, owing to its solubility, is more rapidly absorbed, and consequently acts more quickly than phenacetin. It is said to be more powerfully analgesic, and to be an efficient substitute for salicylates as an antipyretic in acute rheumatism. It may cause collapse and cyanosis. Mosse considers it of value in septic infections only. It is rapidly excreted by the kidneys, so that its action is but transitory.

Salocoll, its salicylic acid compound, is the only salt of phenocoll which is insoluble in water. Its action resembles that of the parent substances.

Class IV.

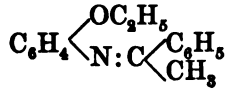
Various condensation products of phenetidin with aldehydes and ketones have been prepared and investigated.

1. Salicyl-phenetidin



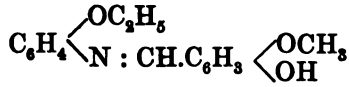
(**Malakin**), is prepared by the action of salicylaldehyde direct or in alcoholic solution on phenetidin. It is almost insoluble in water, and only slightly soluble in alcohol. As an antipyretic, its action is said to be slow, but it is a useful analgesic. The dose is 8–25 grains. Its insolubility interferes with its physiological action.

2. Methyl-benzylidene-phenetidin,



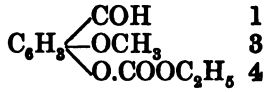
obtained by the action of acetophenone on phenetidin. The citric acid salt of this derivative goes by the name of **Malarin.** The original substance is practically insoluble in water, but freely soluble in hot alcohol. It has a bitter taste, and is employed as an antipyretic and analgesic in doses of 7 grains several times daily. It has considerable action in these directions, but is of little value as a hypnotic as it is markedly toxic, and its action is too precipitate.

3. Vanillin-phenetidin,

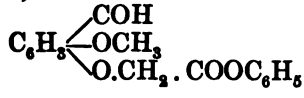


prepared by the action of phenetidin on vanillin, is antipyretic and antiseptic, and also contracts the blood vessels. It is, however, too expensive to be of practical value as a substitute for phenacetin.

Various *p*-amido-phenol derivatives of substituted vanillins have been investigated. Vanillinethyl carbonate, prepared by the action of chlorformic ester on an alcoholic solution of vanillin in presence of potassium hydrate,



or phenacetyl-vanillin,

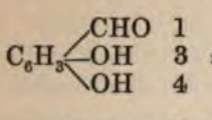


may replace vanillin in these reactions.

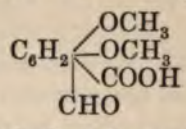
Vanillinethyl-carbonate-*p*-phenetidin has been prepared commercially and is termed **Eupyrin**; it has but slight physiological action.

Vanillin itself is a convulsive agent in animals, but 10 to 15 grains have been given to man without harmful results.

4. In a similar manner to the above, protocatechuic aldehyde,



and opianic acid,

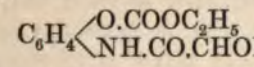


may be condensed with phenetidin; both derivatives have powerful hypnotic properties.

Class V.

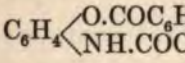
Other groups, besides the radicals of the aliphatic hydrocarbons, have been used to replace the hydroxyl hydrogen atom, thus

1. Lactylamidophenol-ethyl-carbonate,



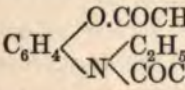
is only slowly decomposed in the organism; it has antipyretic and slight narcotic properties; its toxic action is similar to that of phenacetin or methacetin in similar doses.

2. Acetamidophenol benzoate,



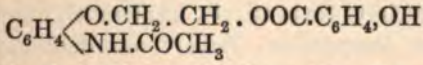
has a weaker action than phenacetin, since its decomposition in the organism only takes place slowly.

3. Acetethylamidophenol acetate,



produces intoxication similar to that produced by ethyl phenacetin; the stage of excitement, however, is more rapidly produced and the narcotic effect less marked. In man it has considerable analgesic and narcotic power, but is only a feeble antipyretic.

4. Oxyphenacetin salicylate



is split up in the body into salicylic acid and probably oxyphe-

nacetin, which is then converted into acetamido phenol. It is said to be of value in rheumatism and neuralgia, but the antipyretic and narcotic actions are very slight, decomposition within the organism taking place slowly.

5. *p*-Acetamidophenoxyl acetamide

$$C_6H_4\begin{cases}O.CH_2.CONH_2\\NH.COCH_3\end{cases}$$

is obtained by the action of monochlor-acetamide on acet-*p*-amido phenol in presence of the calculated amount of alcoholic potash. The corresponding lactyl derivative is obtained in a similar manner from lactyl-*p*-amido-phenol. It has marked antipyretic action.

Class VI.

On its passage through the organism, phenyl urethane, $C_6H_5NH.COOC_2H_5$ (**Euphorin**), is partially converted into *p*-oxyphenyl urethane, and, on the same principles as those previously mentioned, this substance and many of its derivatives have been introduced into pharmacology.

1. *p*-oxyphenyl urethane,

$$C_6H_4\begin{cases}OH\\NH.COOC_2H_5.\end{cases}$$

It is practically non-toxic, but may produce slight rigors.

2. Acetyl-*p*-oxyphenyl urethane (**Neurodin**),

$$C_6H_4\begin{cases}OH\\N\begin{cases}COCH_3\\COOC_2H_5.\end{cases}\end{cases}$$

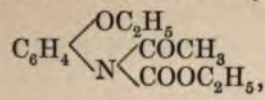
The toxic effects are still further reduced by the entrance of the acetyl group, as are also the antipyretic and analgesic actions. It is very insoluble in cold water, and its antipyretic action, though rapid, is somewhat uncertain.

3. *p*-ethoxyphenyl urethane,

$$C_6H_4\begin{cases}OC_2H_5\\NH.COOC_2H_5,\end{cases}$$

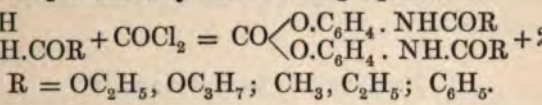
although not free from toxic effects, has a much more certain action in lowering the temperature than those derivatives previously mentioned.

4. The acetyl derivative of this substance,



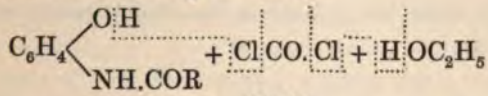
is named **Thermodin.** Its antipyretic effect is said to be gradual, and toxic symptoms have not been observed. It is very insoluble except in acid media, and should therefore be administered combined with acetic acid and syrup, or in some similar way. It is a mild diuretic, but is said to have no depressant action on the heart or respiration in medicinal doses. It is also claimed that it destroys the plasmodium malariae.

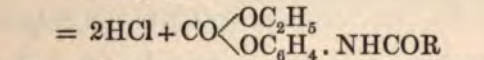
Various derivatives of the oxyphenyl urethane series have been prepared by Merck; one group may be obtained by passing carbonyl chloride into a solution of *p*-oxyphenyl urethane or acid derivatives of *p*-phenetidin in presence of alkali; the reaction which takes place may be represented by the following equation:—



$$R = OC_2H_5,\ OC_3H_7;\ CH_3,\ C_2H_5;\ C_6H_5.$$

If the reaction is carried out in alcoholic solution in presence of sodium alcoholate, mixed carbonates are formed. The reaction may be expressed in the following manner:—





$$R = OC_2H_5,\ OC_3H_7;\ CH_3,\ C_2H_5,\ C_6H_5.$$

On varying the alcohol, the groups methyl or propyl replace ethyl in the above derivatives.

CHAPTER X

THE MAIN GROUP OF SYNTHETIC ANTIPYRETICS (CONTINUED).—*Hydrazine and its derivatives.*—Physiological action of Phenylhydrazine and its derivatives. The Pyrazolon group—Antipyrine, Pyramidon. General Summary of Physiological characteristics of the Ammonia derivatives.

II. DERIVATIVES OF PHENYLHYDRAZINE.

LIKE ammonia, hydrazine, $NH_2—NH_2$, is a strong base and an extremely toxic substance; its most important derivative is phenylhydrazine, $C_6H_5NH—NH_2$, a body which is largely employed in synthetic chemistry.

Preparation and Properties.

Phenyl-hydrazine may be obtained by the reduction of the diazobenzene salts, $C_6H_5N:N.Cl$, through the agency of acid sulphites of the alkalies on the yellow potassium salt of diazobenzene sulphonic acid, whereby colourless potassium benzenehydrazine sulphonate is formed directly,

$$C_6H_5N:N.SO_2OK + KHSO_3 + H_2O = C_6H_5NH.NH.SO_2OK + KHSO_4.$$

When the resulting sulphonate is heated with hydrochloric acid, phenylhydrazine hydrochloride is formed—

$$C_6H_5NH.NH.SO_2OK + HCl + H_2O = C_6H_5NH.NH_2.HCl + KHSO_4.$$

A somewhat simpler method for the preparation of phenylhydrazine consists in the reduction of diazobenzene chloride by stannous chloride,

$$C_6H_5N:N.Cl + 2SnCl_2 + 4HCl = C_6H_5NH.NH.HCl + 2SnCl_4.$$

The double salt of phenylhydrazine hydrochloride and stannic chloride separates out, is decomposed by potash, and the solution extracted with ether; the free base may then be purified by distillation in vacuo.

Phenylhydrazine is a strongly basic substance, more readily

oxidized than aniline; it reduces Fehling's solution, and is a most important reagent for the identification of (i) aldehydes and (ii) ketones, with which it undergoes the following general reactions :—

i. $CH_3.CH{:}O + H_2{:}N.NHPh = H_2O + CH_3.CH : N.NHPh$[1]

Acetaldehyde.

$C_6H_5CH{:}O + H_2{:}N.NHPh = H_2O + C_6H_5CH : N.NHPh$

Benzaldehyde.

ii. $(CH_3)_2C{:}O + H_2{:}N.NHPh = H_2O + (CH_3)_2C : N.NHPh$

$CH_3.C_6H_5C{:}O + H_2{:}N.NHPh = H_2O + CH_3.C_6H_5C : N.NHPh$

The development of the chemistry of the carbohydrates by Emil Fischer was largely based upon reactions similar to these, since that group is entirely composed of ketonic or aldehydic alcohols.

There are few classes of organic substances which lend themselves more readily to the synthesis of ring systems containing nitrogen than do phenylhydrazine and its derivatives. From the pharmacological point of view, the pyrazolon derivatives, among which is antipyrine, are by far the most important, and will be described later.

Physiological Properties.

The reactivity of phenylhydrazine with aldehydes and ketones, together with its powerful reducing action, give it very pronounced toxic properties.

Like hydroxylamine, NH_2OH, hydrazine itself, and to a lesser extent aniline, it brings about destruction of the red blood corpuscles and decomposition of the haemoglobin, besides being a powerful protoplasmic poison. The brown pigment formed in the blood appears to be partly methaemoglobin and partly a substance derived from phenylhydrazine itself (Hoppe-Seyler). Death takes place from general paralysis of cerebral origin, accompanied by convulsions. The admini-

[1] The radical Phenyl, C_6H_5, may be written Ph, Methyl Me, and Ethyl Et.

stration of phenylhydrazine is followed by the appearance of allantoin in the urine. The various attempts which have been made to reduce the toxicity, or rather to bring about a more protracted phenylhydrazine reaction in the organism, follow very closely those employed in the case of aniline.

By a completely corresponding reaction, the stability of the base can be increased by the replacement of the amido hydrogen atom by the acetyl group, but the resulting substance, acetylphenyl-hydrazine, $C_6H_5NH—NH(COCH_3)$ (**Hydracetin**), is still capable of reducing Fehling's solution, although to a less extent than the original substance. Intense depression and collapse, marked fall of temperature, haemoglobinuria, and diminution of the amount of urine excreted, follow even on small doses. Medicinally, only ·2 gram (3 grains) is the maximum dose, so that had it been possible to employ it, it would have been much cheaper than antipyrine.

The intense staining of the tissues after death is evidence of the extent to which haemoglobin is broken up by this substance. It has been employed, like pyrogallic acid, in the treatment of psoriasis, but practically is too toxic even for external application.[1]

Diacetyl phenylhydrazine, $C_6H_5NH—N(COCH_3)_2$, is less toxic, but has a cumulative action as a haemic poison. Thus, though a powerful antipyretic, it is not possible to employ it therapeutically.

In this connexion it may be mentioned that α-β-diacetyl phenylhydrazine,

$$C_6H_5 . N\begin{matrix}\diagup COCH_3 \\ \diagdown NH(COCH_3),\end{matrix}$$

obtained by the interaction of sodium phenylhydrazine, ether, and acetyl chloride, does not appear to have been tried, although from the fact that it is capable of reducing Fehling's solution, its action is not likely to differ much from that of the above-mentioned bodies.

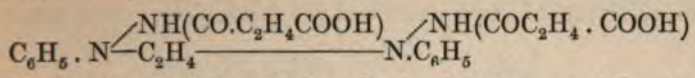
In a very similar manner the amido hydrogen atom has been replaced by the radical benzoyl, but the resulting benzoyl phenylhydrazine, $C_6H_5NH—NH(COC_6H_5)$, acts on the blood in doses that have no action on the central nervous system.

This is also true of ethylene-phenylhydrazine,

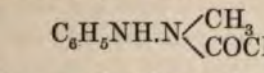
$$C_6H_5 . N\begin{matrix}\diagup NH_2 \\ \diagdown C_2H_4—N.\end{matrix}\begin{matrix}\diagup NH_2 \\ \diagdown C_6H_5\end{matrix}$$

[1] Berl. Klin. Woch., 1899.

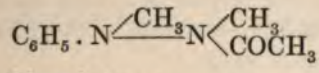
and its succinyl derivative



The relative toxicity of phenylhydrazine is lowered by the replacement of hydrogen by alkyl or acid groups, but the presence of both, as in the case of acetyl- methyl- or ethyl-phenylhydrazine,

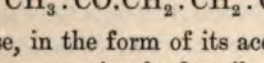


does not decrease the general action on the blood, although the lowering of toxicity is sufficiently marked, and it might be worth while to investigate the physiological reactivity of dimethylacetyl phenylhydrazine,

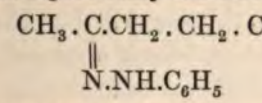


which is a more stable substance.

In the hope of lowering the toxicity attempts have been made to introduce the phenylhydrazine radical into substances containing the acidic (COOH) group. Thus laevulinic acid,

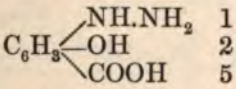


reacts with the base, in the form of its acetate in aqueous solution, in the general manner previously described, yielding the hydrazone



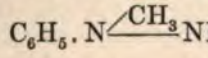
This body has been termed **Antithermin.** Laevulinic acid itself is toxic, and its compound, though actively antipyretic, too poisonous for general use; it is also liable to cause gastric irritation.

Based on the same idea, the substance **Orthin**



has been introduced. The presence of the acid grouping again lowers the toxicity, but the substance is unreliable as an antipyretic and produces undesirable by-effects.

Attempts to modify the action of phenylhydrazine by the introduction of the salicyl residue into α-phenylmethylhydrazine



(which is somewhat less toxic than the unsubstituted base), by means of salicyl aldehyde, result in the formation of the hydrazone

$$C_6H_5.N\overset{CH_2}{\diagup\!\!\diagdown}N:CH.C_6H_4.OH$$

known as **Agathin**, a tasteless, odourless body insoluble in water. But this substance shows its antineuralgic action only in doses of 4–6 gms. (ʒi–ʒiss), a fact which bears out the general observation that salicyl derivatives of this type are only decomposed with such difficulty by the organism that they are unsuitable as antipyretics and antineuralgics. It may produce violent headache.[1]

It will be seen from the above that it has not been found possible to eliminate the powerful action which phenylhydrazine has on the red blood corpuscles, and it does not seem likely that any of the methods described can be so modified as to yield substances of the slightest pharmacological value.

III. PYRAZOLON DERIVATIVES OF THE TYPE OF ANTIPYRINE.

1. Phenyl-3-methyl pyrazolon, the first derivative of this group, was obtained by Knorr, in 1883, through the interaction of phenylhydrazine and acetoacetic ester. The formation of pyrazolon is a general one, and other β-ketonic acid esters react in a similar manner.

As the formation of antipyrine will be easier to follow if the enolic formula[2] for acetoacetic ester is employed,

$$CH_3.C(OH) = CH.COOC_2H_5,$$

this explanation of the reaction will be adopted although its accuracy is perhaps questionable.

The first phase of the reaction consists in the formation of a hydrazone—

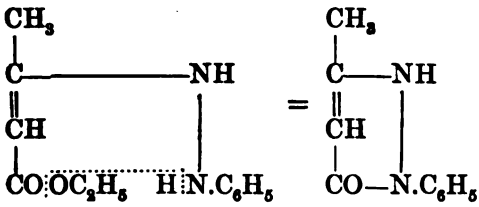
i.
$$\begin{array}{l} CH_3 \\ | \\ C.OH \\ \| \\ CH \\ | \\ COOC_2H_5 \end{array} + H.NH—NHC_6H_5 = \begin{array}{l} CH_3 \\ | \\ C—NH—NHC_6H_5 \\ \| \\ CH \\ | \\ COOC_2H_5 \end{array}$$

[1] *Pharm. Journ.*, vol. xxiii, p. 86.

[2] Acetoacetic ester reacts under certain conditions as if its constitution were expressed by the formula $CH_3.CO.CH_2.COOC_2H_5$; under others, by the formula $CH_3.C(OH):CH.COOC_2H_5$. Such a substance is termed 'Tautomeric' and the first is called the 'Keto' and the second the 'Enol' form.

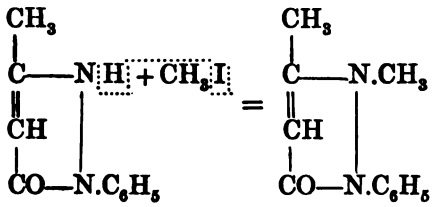
On heating, the resulting substance loses alcohol—

ii.



The body which is formed, 1-phenyl-3-methyl pyrazolon, is converted into antipyrine by heating to 100°–150° C. under pressure with methyl iodide in methyl alcohol solution—

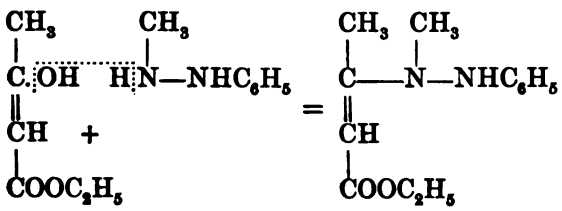
iii.



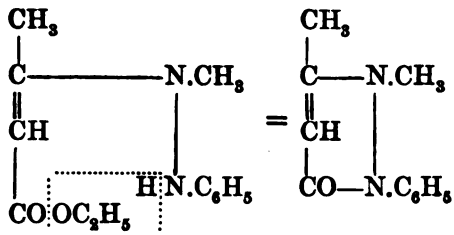
Antipyrine or 1-phenyl-2:3-dimethyl pyrazolon.

This view of its constitution is borne out by its direct synthesis from α-β-phenylmethyl-hydrazine—

1.



2.

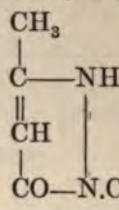


The hydriodic acid salt of antipyrine, which is obtained in the first synthesis, is decomposed by concentrated solution of potash. Antipyrine dissolved out by chloroform or benzene is recrystallized from ether.

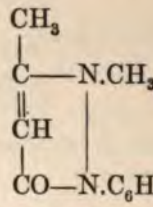
Many modifications of this synthesis have been made since its discovery, and will be found in the larger textbooks on organic chemistry.

Physiological Properties of Antipyrine and its derivatives.

It is interesting to note that the characteristic antipyrine properties are entirely absent in 1-phenyl-3-methyl pyrazolon,



and it is only when the imido hydrogen atom is replaced by methyl, that these appear: –



With **Antipyrine (Phenazone)** the paralysing action on the motor centres in the mid brain is not well marked. It is not narcotic, but in large doses it produces destruction of haemoglobin, collapse, and convulsions. The latter are well marked in frogs with doses of from 50–60 mgm. It has the great advantage of easy solubility in water. Its antipyretic action is not due to any influence on the oxygen capacity of the blood. Sweating, as accelerating heat-loss, also has but a small share, for the fall of temperature produced by antipyrine occurs when sweating has been prevented by belladonna. It does not act, however, when the higher parts of the brain are cut off by section through the cord or through the crus cerebri. In fever experimentally produced by damage to the corpus striatum antipyrine produces a fall of temperature.

Most probably this effect is due to the dilatation of the cutaneous vessels and a consequent increase of heat-loss.

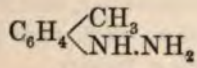
In some animals (including man) the thermotaxic centre is so stimulated by this process that heat production is forthwith increased as a compensatory measure. In man, also, there is a decrease in the respiratory activity.

Nitrogenous metabolism, which is practically uninfluenced in health, is decreased in pyrexial conditions when this drug is administered. This is not a direct action, but is dependent merely on the antipyretic effect of the drug, which cannot influence the increased nitrogen waste due to toxic processes.

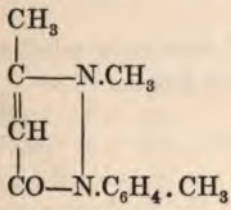
As an analgesic, it is largely used, and the number of cases in which bad by-effects have occurred does not appear to be great. When first introduced, Sèe gave 15 grains every hour up to 50 or 100 grains, but it is not now given in these large doses. In cases in which unpleasant symptoms (collapse, oedema, rashes, &c.) have appeared, these have not always been the result of large doses. Guttmann reports a case in which a man took 15 grains of antipyrine in five days, which produced a condition closely resembling cholera, except that diarrhoea was not present, and there was a dusky rash on the abdomen.

Antipyrine is found in the urine to some extent unchanged, but chiefly as a glycuronic acid derivative; most probably oxidation, with the formation of oxyantipyrine, precedes this synthesis.

When *p*-tolyl hydrazine



is employed in the pyrazolon synthesis, instead of the phenyl derivative, **Tolylpyrine**



is obtained. It is more irritating than antipyrine, and affects the circulation unfavourably, while its analgesic action is not so pronounced.

The salicylic acid salts of both antipyrine and tolylpyrine have been introduced under the names of **Salipyrine** and **Tolysal.** These are obtained by melting together the constituents on the water bath; the resulting derivatives contain a free carboxyl group, and from them a series of salts may be obtained. They are readily decomposed into their constituents by hydrochloric acid, and their

[1] *Pharm. Journ.*, vol. xxiii. p. 605.

physiological reaction corresponds to that of a mixture of antipyrine and salicylic acid.

Several derivatives of this type have been introduced into pharmacology, for example:—

Tussol is the mandelic acid ($C_6H_5CH.OH.COOH$) salt of antipyrine. It has been given as a remedy for whooping cough in doses of 15–30 cgms. per diem for children under one year, and more proportionately to age for older children. There is no evidence that it is superior to antipyrine, which is well tolerated by children.

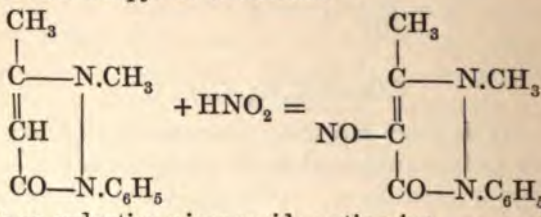
Hypnal, or **Hypnol,** is a compound of chloralhydrate and antipyrine. It is said to be more soporific and to have less action on the circulation than chloral, but its general toxicity is higher. Bichloral-antipyrine is still more toxic, and has no advantages over chloral or hypnal.[1]

Anilopyrine (Acetanilide and antipyrine) is a soluble white powder, but apparently has no particular advantage over a mixture of the two bodies which has long been a favourite prescription for neuralgia and headaches of various sorts.

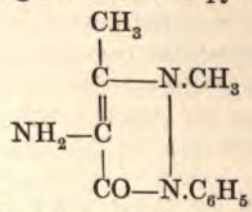
Bodies of this type, owing to the ease with which they are decomposed, can only act as mixtures, and it is consequently fruitless to search for substances with new physiological reactions amongst derivatives of such a nature.

Pyramidon, or 4-dimethylamido-antipyrine, is the only antipyrine derivative which has proved of value. It is obtained by the following reactions:—

1. When nitrous acid acts on a solution of antipyrine hydrochloride, nitroso-antipyrine is obtained—

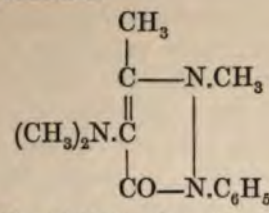


2. This on reduction gives amido antipyrine,

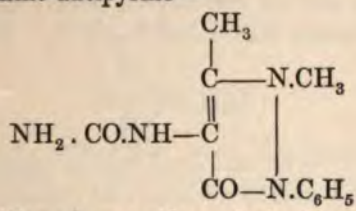


[1] *Pharm. Journ.*, vol. xxi, p. 161.

which is isolated by means of its benzylidene derivative, and on methylation gives **Pyramidon**—



Pyramidon is a solid which dissolves in water, giving an alkaline solution, and is a more powerful base than antipyrine. The dose is about one-third that usually given in the case of the latter drug. It has no irritant effect on the stomach, and may also be prescribed in nephritis and heart disease, as its effect on the circulation is but slight. It is not a blood poison. It has been used on the continent both as an antipyretic and an analgesic, but in this country its use is mainly as a drug of the latter class. It is excreted in the urine partly unchanged, partly as glycuronic acid, and partly as uramino-antipyrine—



After the exhibition of pyramidon a derivative occasionally appears in the urine which, on standing, becomes oxidized and produces the red colouring matter, rubazonic acid.

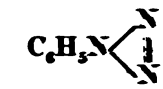
It has been suggested that pyramidon should not be given to diabetics, as, contrary to the general run of antipyrine derivatives, it increases nitrogenous metabolism.

GENERAL SUMMARY OF THE PHYSIOLOGICAL CHARACTERISTICS OF THE AMMONIA DERIVATIVES.

The three substances, antifebrin, phenacetin, and antipyrine (phenazone) may be taken as representative of the entire series of synthetic antipyretics which have just been described. They are not only chemically representative bodies, but therapeutically they are probably more valuable than all the other members of the classes to which they belong put together. From the pharmacological point of view they may be considered as true antipyretics;

that is to say, they so influence the thermotaxic centre that it causes a general cutaneous vaso-dilatation to take place during pyrexia, thus producing increased heat-loss and a fall in temperature. That they are not mere general vaso-dilators is shown by the fact that the deep vessels are not affected. This, a central action, is very different physiologically from the effect produced by the external application of cold, when heat-loss is increased, but the thermotaxic centre is uninfluenced. In health, the thermotaxic centre maintains a certain fairly constant ratio between heat-production and heat-loss: in pyrexia this ratio is altered, and increased heat-production does not lead to a sufficient increase in heat-loss; the true antipyretics so influence or sensitize the thermotaxic centre that the ratio tends to return to normal. This may or may not be a valuable measure therapeutically; at present the tendency is to consider it disadvantageous to reduce the temperature in this way, and the antipyretic drugs are mainly used for other purposes.

The antipyretic action is a function of the benzene nucleus, for it is shared by such varied derivatives as phenol, pyrocatechin, salicyl acid, aniline and its derivatives, phenyl hydrazine, and the aromatic semi-carbazides $R.NH.NH.CO.NH_2$. Phenyl-azo-imide,



also acts as an antipyretic and analgesic in mammals. Moreover, other ring formations, such as pyridine and quinoline, have the same physiological action.

On the other hand, all ring compounds are not active antipyretics. The ethyl ester of α-naphthylazoacetoacetic acid,

$$C_{10}H_7N : N\,CH\langle \begin{matrix} COCH_3 \\ COOC_2H_5 \end{matrix},$$

α-acetone-naphthalide and phenanthren, are examples of inactive substances with ring structures.

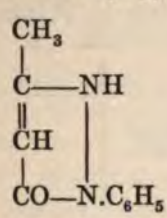
The side-chains in the above-mentioned compounds vary so much that it is clear that no importance can be attached to them as antipyretic agents. Their function is possibly to enable the molecule to anchor itself to the cells in the central nervous system, and for this purpose the basic chains are more suitable than the acid. Aniline is a more powerful antipyretic than phenol, but less powerful than phenylhydrazine; the latter owes its physiological activity partly to its chemical instability.

The second therapeutic action of these bodies, which, as has

previously been noted is at present the most generally employed, is the analgesic and slightly hypnotic powers which they possess. This is not solely due to the benzene ring, but is apparently the result of two factors, either jointly or separately. One factor is the presence of the ketonic group, such as $CH_3.CO.NH.R$. Ethyl-ketone, acetophenone, and other ketones are hypnotics. The second factor is the ethoxy group, which apparently accounts for the hypnotic effect in some of the *p*-amino-phenol derivatives, whilst in lactophenin and some other bodies both these factors are united.

The two main groups may now be considered in detail, as they present different points of interest corresponding to their chemical structure.

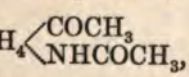
The group of which antipyrine and pyramidon are types owes its antipyretic properties to the ring formation, which contains a nitrogen element. The monomethyl pyrazolon



is not antipyretic; in antipyrine itself the second methyl group replacing the hydrogen of the imido radical apparently therefore acts as an anchoring group.

The phenyl radical apparently intensifies the action; some antipyretic effect can be obtained without it; in view, however, of the known antipyretic effect of benzene, the pyrazolon ring might be regarded as intensifying this by the substitution of one of the hydrogen atoms. The introduction of the basic group (in pyramidon) increases the reaction. *iso*-Pyrazolon derivatives are toxic, but not antipyretic.

The aniline and *para*-amino-phenol derivatives can be considered together, as the action depends on the liberation of the latter in the organism. Acetyl-*p*-amino-acetophenone,



has no antipyretic action, because the *para* group, $COCH_3$, prevents the formation of $C_6H_4OH.NH_2$. These bodies may be regarded as designed to produce a slow and gradual aniline or *p*-amino-phenol

reaction; they are, as it were, *methods of dosage*. This being so, it is obvious that those compounds from which the parent substance is slowly evolved will be little toxic and also less efficient as antipyretics, whereas the powerful antipyretics will always be dangerous in practice.

The toxic properties of these substances may be specified as (1) a general action on the central nervous system, and (2) a special action on the blood (disintegration of the red cells and formation of methaemoglobin). The general toxic action is practically the same for aniline and phenol, and differs in degree only owing to the fact that primary amines are more active physiologically than alcohols. There is, however, no general agreement in the relative toxicity of the two series of compounds, though as a general rule those which contain but one side-chain are the most toxic. The length of the side-chains also has a certain influence.

The following table is given by Fränkel:—

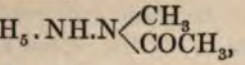
Phenol series.			Aniline series.		
	Average toxic dose in gms.	Physiological action.		Average toxic dose in gms.	Physiological action.
Phenol	·045 – ·055	convulsions and rigors.	*Aniline*	·051 – ·52	convulsions and rigors.
Cresol	·02 – ·035 *p>o>m*	convulsions and rigors.	*Toluidine*	·052 – ·089 *p>m>o*	convulsions and rigors.
Anisol	·35 – ·40	slight convulsions, no rigors.	*Methylaniline*	·37 – ·40	slight convulsions, no rigors.
Benzyl alcohol	·17	no convulsions, no rigors.	*Benzyl amine*	·25 – ·5	characteristic rigors.
Oxyphenol	·2 – ·05 *o>p>m*	convulsions and rigors.	*Phenylene-diamine*	·015 – ·05 *o>p>m*	no convulsions, no rigors.
Oxybenzoic acid	·09 – ·1	convulsions.	*Amidobenzoic acid*	·2 – ·6 *o>m>p*	no convulsions.

The action as blood poisons is dependent on the presence of the basic group; hence phenylhydrazine is more active than aniline in this respect; ammonia and, still more, hydroxylamine and hydrazine produce the same effect. The substitution of the two hydrogen atoms of the base does not necessarily modify this action.

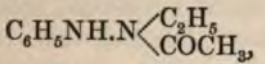
Exalgin,

$$C_6H_5N\begin{matrix}CH_3\\COCH_3,\end{matrix}$$

acetyl-methyl-phenylhydrazine,

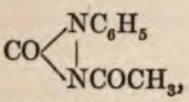


and acetyl-ethyl-phenylhydrazine,

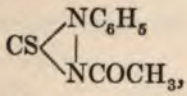


are all active blood poisons.

Even if all the free hydrogen atoms are substituted, as in acetyl-phenyl-carbazine,



and acetyl-phenyl-thiocarbazine,



the action on the blood takes place, even with doses too small to have any influence on the central nervous system.

With regard to phenacetin, the steps in its construction are as follows:—*p*-Amido-phenol is less toxic than aniline; but it is unstable and still fairly toxic. The introduction of an acyl group into the basic substituent does not render the substance sufficiently stable to prevent a rapid formation of *p*-amido-phenol in the body; but if in addition the hydrogen of the hydroxyl group is substituted, a useful combination can be obtained. All the bodies so formed depend for their action on phenetidin or *p*-amido-phenol formation; and, if active, are characterized by the production of the indol reaction in the urine. If this reaction fails, the drug must be considered inert. Bodies, on the other hand, which are of the nature of salts of phenetidin, or on which the hydrochloric acid in the stomach can act so as to produce a salt, are too toxic and cannot be safely employed.

Of the many acyl substitution products of phenetidin which have been introduced phenacetin probably produces the maximum physiological effect with the minimum of toxicity. The only objection to it is its insolubility; but when this is overcome, as in lactophenin, the toxicity is at once increased owing to the hydrochloride of phenetidin being formed in the stomach.

The replacement of the hydrogen of the amido group in phenetidin by an aromatic radical produces too stable a compound, with-

out physiological action; the substitution of the hydrogen of the hydroxyl group by an aliphatic acid produces too unstable a compound, with toxic action. If the second hydrogen atom of the basic residue in phenacetin is replaced by an alkyl group a narcosis similar to that produced by alcohol occurs; an acid group in this place is so easily detached that it has no physiological importance.

Compounds derived from *ortho*- or *meta*-phenetidin are too toxic for practical purposes.

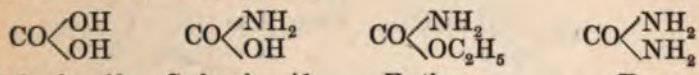
CHAPTER XI

I. The Group of Urethanes, Urea and Ureides.—Urethane. Hedonal. Hypnotics derived from Urea. Thio-urea. Thiosinamine. Veronal hypnotics.

II. The Purine Group and Pilocarpine.—Diuretics and Cardiac tonics. Modification of substances of Xanthine type. Diaphoretics. Pilocarpine.

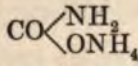
I. THE GROUP OF URETHANES, UREA, AND THE UREIDES.

Carbonic acid forms amides, which are in all respects analogous to those of a dibasic acid, thus—



Carbonic acid. Carbamic acid. Urethane. Urea.

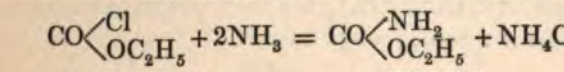
A. Carbamic acid is unknown in the free state, but its ammonium salt,



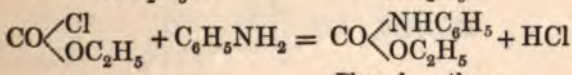
is present in commercial ammonium carbonate. This substance is toxic, probably owing to its very labile character, and produces symptoms similar to those caused by ammonia. But its esters, the urethanes, are much more stable and consequently less toxic; they possess, moreover, hypnotic properties depending upon the nature of the organic radical replacing the hydroxyl hydrogen.

A. The Urethanes.

The urethanes are obtained by the action of ammonia or the substituted ammonias, on the esters of chlor-carbonic acid[1]:



or



Phenyl urethane, or Euphorin.

[1] This method of introducing the ($COOC_2H_5$) radical into basic or other substances, with the resulting depression of toxicity, is one often employed (p. 130).

and by the action of heat on a mixture of urea nitrate and the corresponding alcohol,

$$CO\langle^{NH_2}_{NH_2} + CH_3.CHOH.C_3H_7 = NH_3 + CO\langle^{NH_2}_{O.CH\langle^{CH_3}_{C_3H_7}}$$

Methyl-propyl-carbinol.

Methyl-propyl-carbinol-urethane. **Hedonal.**

Physiological Properties.

Binet has found that the physiological reactivity of these derivatives increases according to the magnitude of the alcohol radical. The introduction of the acetyl group lowers the toxicity without otherwise altering the physiological action. In the case of warm-blooded animals, the relative toxicity of these substances is as follows :—

$CO\langle^{NH.COCH_3}_{O.R}$ when $R = CH_3$ 1
„ $R = C_2H_5$ 1·5

$CO\langle^{NH_2}_{O.X}$ when $X = CH_3$ . . . 2
„ $X = C_2H_5$ . . 4

Urethane, $CO\langle^{NH_2}_{OC_2H_5}$,

in spite of the presence of an amido group, has no depressant effect on the respiratory centre; on the contrary, it has some stimulant action, but only in doses which exceed those given therapeutically. It has no action on blood pressure or on the pulse rate, and is markedly diuretic, like all the urea derivatives. Its hypnotic action is rapid, but not sufficiently powerful for use in cases where there is any pain or distress. Even in large doses it does not appear in the urine, but is apparently converted into urea. Small doses are said to decrease nitrogenous metabolism, whereas large doses have a contrary effect.

Di-urethane, $NH(COOC_2H_5)_2$, is a more powerful narcotic, owing to the presence of a second alkyl radical.

Hedonal, $CO\langle^{NH_2}_{O.CH\langle^{CH_3}_{C_3H_7}}$,

acts similarly to urethane, being narcotic and powerfully diuretic. The dose is double that of chloral. It has been employed as a preliminary to general anaesthesia with chloroform; its absorption is slow, and it must be given at least an hour before the

anaesthetic. There are, however, other more serious objections to its practical employment in this manner.

B. Urea and its Derivatives.

Urea, $CO\langle^{NH_2}_{NH_2}$

was first synthesized by Wöhler in 1828 from ammonium *iso*-cyanate, which undergoes an intra-molecular transposition on the evaporation of its aqueous solution—

$$CO:N.NH_4 \rightarrow CO\langle^{NH_2}_{NH_2}$$

It is found in various animal fluids, chiefly in the urine of mammals, and may be separated as the somewhat insoluble nitrate.

It may also be prepared by the following synthetic processes:—

1. $CO\langle^{NH_2}_{OC_2H_5} + NH_3 = C_2H_5OH + CO\langle^{NH_2}_{NH_2}$
   Urethane.
2. $CO\langle^{OC_2H_5}_{OC_2H_5} + 2NH_3 = 2C_2H_5OH + CO\langle^{NH_2}_{NH_2}$
   Diethyl-carbonate.
3. $CO\langle^{Cl}_{OC_2H_5} + 3NH_3 = C_2H_5OH + NH_4Cl + CO\langle^{NH_2}_{NH_2}$
   Chlorformic ester.

Urea crystallizes in long needles, or rhombic prisms, which have a cooling taste. It is soluble in 1 part cold water, 5 of alcohol, but almost insoluble in ether. It is decomposed by nitrous acid, as are all substances containing the amido group.

$$CO\langle^{NH_2}_{NH_2} + 2HNO_3 = CO\langle^{OH}_{OH} + 2N_2 + 3H_2O.$$

The **Alkyl Ureas** may be prepared by reactions similar to those employed in the case of urea itself.

1. Mono-alkyl ureas.

$$CO\langle^{NH_2}_{OC_2H_5} + C_2H_5NH_2 = CO\langle^{NH_2}_{NHC_2H_5} + C_2H_5OH$$

Urethane. Ethyl-amine. Ethyl urea.

2. Di-alkyl ureas.

   A. Unsymmetrical.

$$CO\langle^{NH_2}_{OC_2H_5} + (C_2H_5)_2NH = CO\langle^{NH_2}_{N(C_2H_5)_2} + C_2H_5OH$$

Diethyl-amine. *a*-Diethyl urea.

B. Symmetrical.

i. $CO\langle^{OC_2H_5}_{OC_2H_5} + 2C_2H_5.NH_2 = CO\langle^{NHC_2H_5}_{NHC_2H_5} + C_2H_5OH$

S. Diethyl urea.

ii. $CO\langle^{Cl}_{OC_2H_5} + 2C_2H_5NH_2 = CO\langle^{NHC_2H_5}_{NHC_2H_5} + 2C_2H_5OH$

Chlorformic ester.

3. Tetra-alkyl urea.

$$CO\langle^{OC_2H_5}_{OC_2H_5} + 2(C_2H_5)_2NH = CO\langle^{N(C_2H_5)_2}_{N(C_2H_5)_2} + 2C_2H_5OH$$

Tetra-ethyl urea.

The alkyl ureas are crystalline substances, with the exception of the tetra substitution derivatives, and show the same characteristic reactions and properties as urea itself, and, like it, form salts with one equivalent of acid.

Physiological Properties.

Urea has but slight toxic properties for animals or higher plants. It has no action at all on the lower plants. Its chief effect in the animal body is to produce diuresis, and it also has a very slight narcotic action. Toxic doses (injections of $\frac{1}{100}$ the total body-weight in rabbits) produce spasms and opisthotonos. Ammonia is not set free in the blood.

When the hydrogen of the amido group is replaced, it is found that the simple alkyl ureas have no narcotic action; with those containing tertiary alkyl groups the general characteristic is observed (see p. 92), viz. that a tertiary system containing methyl groups, such as

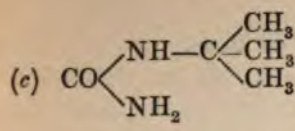
$$-C\langle^{CH_3}_{CH_3}_{CH_3}$$

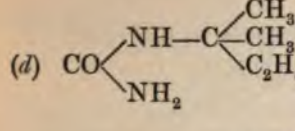
is less reactive than those containing ethyl, such as

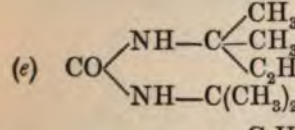
$-C\langle^{C_2H_5}_{CH_3}_{CH_3}$ tertiary butyl or tertiary heptyl, $-C\langle^{C_2H_5}_{C_2H_5}_{C_2H_5}$

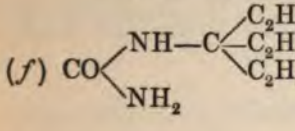
(*a*) $CO\langle^{NHC_2H_5}_{NH_2}$ 3–4 gms. without action.

(*b*) $CO\langle^{N(C_2H_5)_2}_{NHC_2H_5}$ 3 gms. produce drowsiness, but no sleep. Inactive ethylamine bases are apparently set free in the body.

(*c*)  4 gms. produce sleep.

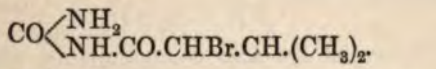
(*d*)  This is more active than amylene hydrate as a hypnotic; but sleep occurs later, owing to the fact that this derivative, which is not easily soluble, takes longer to decompose.

(*e*)  This body passes into the urine unchanged. It is very stable, and has no physiological action.

(*f*)  1 gm. produces sleep after 2 hours, preceded by a period of intoxication. It is not very soluble.

Urea Derivative containing Bromine.

The *α*-monobrom-*iso*-valeryl urea has been introduced by Saam under the name of **Bromural**—



It is not easily soluble in cold, but dissolves readily in hot water, ether, alcohol, and weak alkalies; Saam thinks that the narcotic action of this drug depends upon three factors. The main hypnotic is the *iso*-propyl radical in the valerianic acid, but its action is intensified, firstly by the presence of the urea grouping, and secondly by the bromine atom. The corresponding chlorine compound is but slightly hypnotic, the iodine compound is inactive. The lethal dose for rabbits begins at 1 gm. per kilo. body-weight; in dogs, ·5 gm. per kilo. produced toxic effects, mainly on the respiration, while larger doses produced death from respiratory failure, the heart remaining unaffected. The hypnotic action is mild, and is interfered with by the presence of pain, cough, or active delirium.

Sulphur Derivatives of Urea.

Thio-urea or sulphocarbamine,

$$CS\langle^{NH_2}_{NH_2}$$

is obtained by heating ammonium thio-cyanate to 170°–180° C.

$$CS : N.NH_4 \rightarrow CS\langle^{NH_2}_{NH_2}$$

Many of its reactions indicate a constitution expressed by the formula—

$$HN : C\langle^{NH_2}_{SH}$$

It causes slowing of the pulse and respiration, and brings about general paralysis of central origin, cardiac failure, and death in convulsions.

Allyl-thio-urea $CS\langle^{NH_2}_{NH.CH_2}.\ CH : CH_2$

Phenyl-thio-urea $CS\langle^{NH_2}_{NHC_6H_5}$

Ethyl-thio-urea $CS\langle^{NH_2}_{NHC_2H_5}$

Acetyl-thio-urea $CS\langle^{NH_2}_{NH.(CH_3CO)}$

are actively toxic, as are also compounds in which both amino groups are substituted with different radicals, e. g.

Allyl-phenyl-thio-urea $CS\langle^{NHCH_2 : CH.CH_2}_{NHC_6H_5}$

Methyl-ethyl-thio-urea $CS\langle^{NHCH_3}_{NHC_2H_5}$

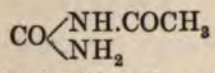
The symmetrical compounds, however, like urea itself, and dimethyl or diphenyl urea have only very slight physiological action.

Of these bodies, allyl-thio-urea, or **Thiosinamine,** is the only one of pharmacological importance. In toxic doses it produces narcosis, death occurring with oedema of the lungs and hydrothorax. Very small doses excite the central nervous system, larger doses depress it. Thiosinamine appears to have a characteristic action on organized scar tissue. When injected subcutaneously it causes absorption and softening of cicatricial bands and adhesions. This action, however, does not appear to be constant.

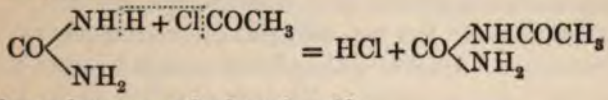
C. The Ureides.

The ureides are the urea derivatives of organic acids, and may belong to one of two groups.

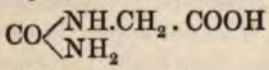
A. Those containing open chains, such as acetyl-urea, previously alluded to,



a substance which is obtained by the action of acid chlorides, or anhydride, on urea, thus :—

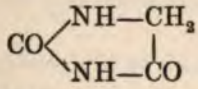


or such a substance as hydantoic acid,

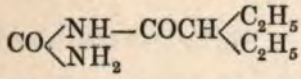


the open-chain ureide of glycollic acid.

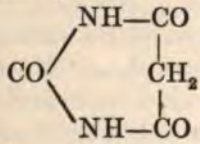
B. Those containing a ring-shaped structure or cyclic ureides, such as hydantoin,



Emil Fischer and J. v. Mering have prepared substances belonging to these groups, and considering the fact that the hypnotic action appears to be so largely dependent on the presence of ethyl groups, they investigated the following : diethyl-acetyl-urea,

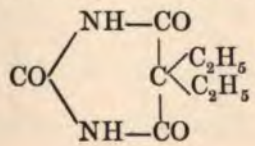


belonging to the first class ; and two derivatives of malonyl-urea,

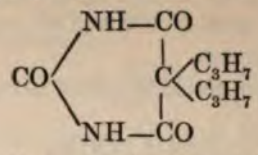


belonging to the second.

These two derivatives are diethyl-malonyl-urea



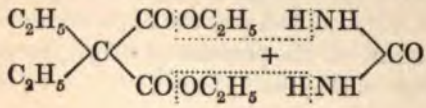
and the corresponding dipropyl-malonyl-urea—



They state that of the series investigated 'the three mentioned stand out prominently in point of hypnotic action . . . and experiments have shown that diethyl-acetyl-urea is about equal in hypnotic power to sulphonal, that dipropyl-malonyl-urea is about four times as powerful, but not infrequently has a remarkably prolonged after-effect. Diethyl-malonyl-urea stands midway between these two, and hence surpasses in intensity of action all the hitherto employed hypnotics. Inasmuch as it has advantages with regard to taste and solubility, it would appear to be the most valuable of these new derivatives for therapeutic purposes.'

This substance, which goes by the name of **Veronal,** is stated to be a prompt hypnotic, and it may be mentioned that the effective dose of veronal costs less than that of Trional, or any other hypnotic excepting chloral hydrate.

Veronal may be obtained by the condensation of diethylmalonic acid with urea in presence of sodium ethylate,

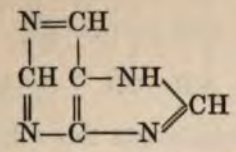


$$= 2C_2H_5OH + (C_2H_5)_2{-}C\begin{matrix}CO{-}NH\\CO{-}NH\end{matrix}CO.$$

Veronal is also a diuretic, but it has no irritant action on the kidneys. It does not influence the blood pressure or depress the heart. It has no action on the gastro-intestinal mucosa. It is said to diminish nitrogenous metabolism. The toxicity is low, 9 gms. (135 grains) having been taken in a single dose without serious results; ·7 gm. per kilogram body-weight can be given to animals before a direct toxic action occurs.

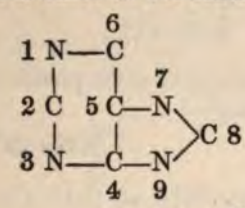
II. THE PURINE GROUP.

The compounds of this group are all derived from the substance purine—

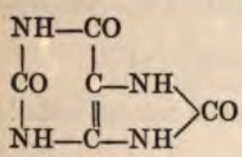


This complex is found in a large number of the products of animal and plant life, namely, uric acid, xanthine, guanine, theobromine (found in cocoa beans), caffeine, &c.

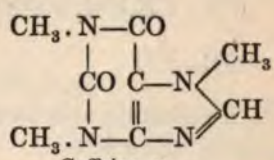
Their nomenclature is based on the scheme



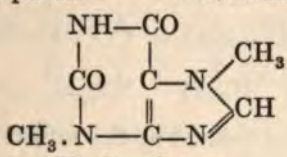
thus:



Uric acid or
2:6:8-triketo-purine.



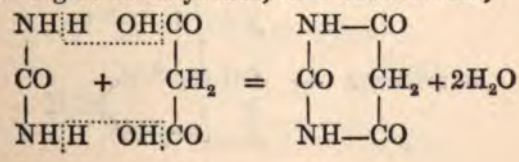
Caffeine or
1:3:7-trimethyl-2:6-diketo-purine.



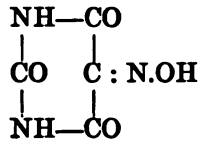
Theobromine or
3:7-dimethyl-2:6-diketo-purine.

The systematic investigation of this group was carried out by Emil Fischer and his students, and the following synthesis of uric acid will give some idea of the general method adopted.

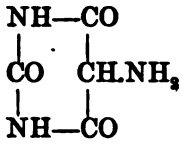
1. Malonic acid condenses with urea in presence of phosphorus oxychloride to give malonyl-urea, or barbituric acid,



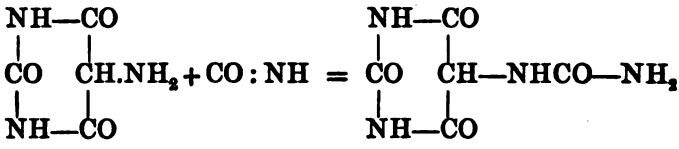
2. Malonyl-urea is converted into an *iso*-nitroso derivative by means of nitrous acid—



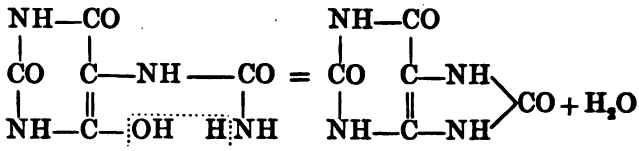
3. Reduced with hydriodic acid this substance gives the corresponding amido derivative



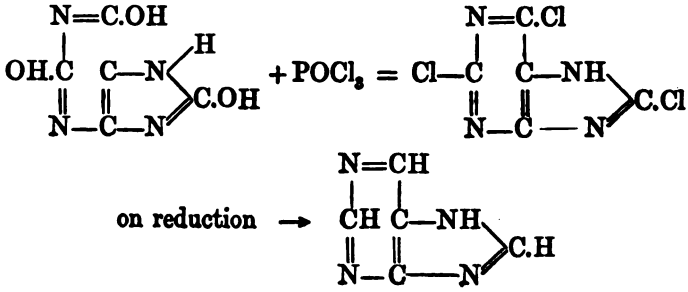
4. This amido-barbituric acid gives pseudo-uric acid on treatment with potassium cyanate—



5. Pseudo-uric acid treated with dilute mineral acids loses water and gives uric acid—



Purine itself may be isolated by the reduction of 2 : 6 : 8-trichlorpurine, obtained by the action of phosphorus oxychloride on potassium urate—



Theophylline, which Kossel found in tea, may be synthesized from dimethyl-urea in a manner very similar to the above:—

1. $CH_3—NH\ OH:CO$ / CO + CH_2 / $CH_3.NH\ OH:CO$ $= 2H_2O +$ $CH_3—N—CO$ / $CO\ CH_2$ / $CH_3—N—CO$

2. $CH_3—N—CO$ / $CO\ CH_2 + HNO_2 =$ / $CH_3.N—CO$ $CH_3.N—CO$ / $CO\ C:N.OH + H_2O$ / $CH_3.N—CO$

3. $CH_3—N—CO$ / $CO\ C:N.OH + 4H \rightarrow$ / $CH_3.N—CO$ $CH_3—N—CO$ / $CO\ CHNH_2$ / $CH_3—N—CO$

This derivative acted upon with $CO:NH =$ $CH_3—N—CO$ / $CO\ CH—NH—CO—NH_2$ / $CH_3—N—CO$

1:3-dimethyl-pseudo-uric acid.

4. $CH_3—N—CO$ / $CO\ C—NH—CO = H_2O +$ / $CH_3—N—C.OH\ H:NH$ $CH_3.N—CO$ / $CO\ C—NH$ (>CO) / $CH_3.N—C—NH$

1:3-Dimethyl uric acid, or 1:3-Dimethyl-2:6:9-triketo-purine.

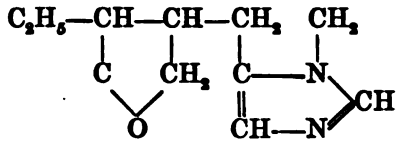
5. When this uric acid derivative is treated with chloride of phosphorus, and the resulting substance reduced, theophylline is formed.

$CH_3—N—CO$ / $CO\ C—NH$ (>CO) / $CH_3.N—C—NH$ $\xrightarrow{POCl_3}$ $CH_3—N—CO$ / $CO\ C—NH$ (>CCl) / $CH_3—N—C—N$

$\xrightarrow{\text{reduced}}$ $CH_3—N—CO$ / $CO\ C.NH$ (>CH) / $CH_3.N—C.N$

Theophylline, or 1:3-dimethyl-2:6-diketo-purine.

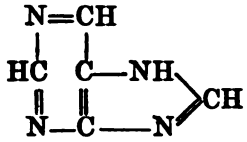
Pilocarpine has been introduced into this group, although it does not contain the purine complex. Like theobromine, theophylline, and caffeine, it contains a glyoxalin ring. Jaborandi leaves contain three alkaloids, pilocarpine, pilocarpidine and jaborine, and the most recent researches point the following constitutional formula for the first substance:—



the presence of the glyoxalin ring being shown by the many relationships pilocarpine bears to the methylglyoxalin derivatives.

Physiological Reactions of Purine Derivatives.

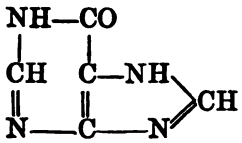
Purine itself



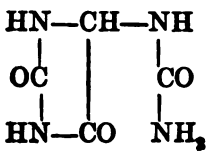
acts on the cerebrum like the ammonium salts, and has a tendency to produce convulsions. It also produces rigidity of the muscles. These actions it transmits to its derivatives, caffeine and theobromine.

A. Oxy-derivatives.

6-Oxy-purine



(**Hypoxanthine, Sarcine**), has a power of producing tetanic spasms, but no rigidity; in dogs, it is said to be largely oxidized into allantoine,



This substance, however, is stated by Baldi to increase the excitability of the spinal cord, and to produce muscular rigidity in frogs. Walker Hall injected rabbits daily for two months with small doses, and found degenerative changes in the liver cells and alterations in the bone marrow.

In man, hypoxanthine is excreted mainly as uric acid. It is said to act in about six hours, producing increased reflex irritability and spontaneous spasms, and then general tonic contractions. 50–100 mgms. constitute a fatal dose for dogs.

8-Oxypurine produces no tetanus, but only muscular rigidity. Its action is but feeble.

B. Alkyl and Oxyalkyl Derivatives.

To pass on to the corresponding methyl derivatives, 7-methyl-purine acts more powerfully on the muscles than purine, but is nevertheless a weak poison. 1 gram subcutaneously has no action on dogs.

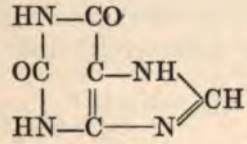
1 : 7-Dimethyl-6-oxypurine is a tetanizing agent, and also produces rigidity in frogs, but acts less powerfully than caffeine.

7 : 9-Dimethyl-8-oxypurine produces both muscular rigidity and tonic convulsions similarly to the previous compound, and the differences between the two monoxypurines, from which they are derived, are probably due merely to differences in rate of absorption.

C. Dioxy Derivatives.

6 : 8-Dioxypurine is too insoluble to have any marked action, but is said to have some action on the central nervous system.

Xanthine, 2 : 6-dioxy-purine,



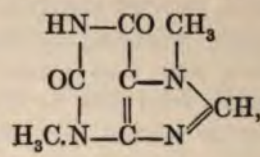
has no marked diuretic action, but may produce haematuria. It has the same action on muscle and spinal cord as 8-oxypurine.

D. Dioxy-alkyl Derivatives.

The two monomethyl-xanthines act similarly to caffeine and theobromine, both on the muscles and on the nervous system, but are more powerful tonic convulsants.

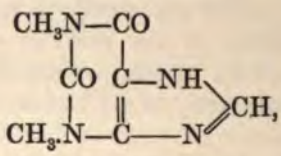
Heteroxanthine (7-methyl-xanthine) has more paralysing action on the cord than 3-methyl-xanthine, and is generally more powerful, though it does not raise the reflex excitability so much. The 3-methyl-xanthine is a diuretic for dogs.

Theobromine, 3 7-dimethyl-2 : 6-dioxypurine,



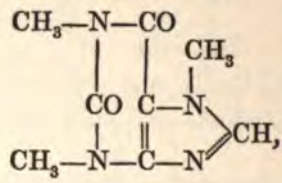
is a very powerful diuretic. Its action on the activity and irritability of muscle resembles that of caffeine, but it has no vaso-constrictor action. In toxic doses it produces more rigidity, but not such severe convulsions as caffeine. Like xanthine, it has a direct coagulating action on muscular protoplasm, but unlike xanthine it has no action on the heart.

Theophyllin (1 : 3-dimethyl-2 : 6-dioxypurin), known also by its trade name **Theocine**,



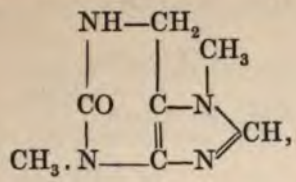
is a more powerful diuretic; it has no action on the heart or central nervous system, but acts more markedly on muscle than theobromine. Its diuretic effect is said not to last so long as that of theobromine. In two cases it produced gastric haemorrhage and death; this was also observed experimentally in animals.

Paraxanthine (1:7-dimethyl-2:6-dioxypurine),



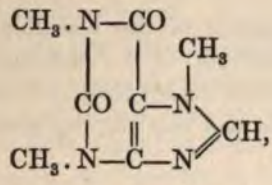
has a yet more powerful diuretic action, and also produces more muscular rigidity and paralysis than either of the other two dimethyldioxypurines.

Desoxytheobromine (3:7-dimethyl-2-oxy-1:6-dihydropurine),



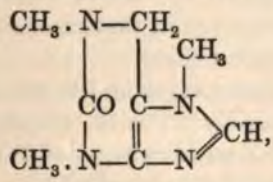
in large doses diminishes the urinary excretion, but is inactive otherwise.

Caffeine is 1:3:7-trimethyl-xanthine,



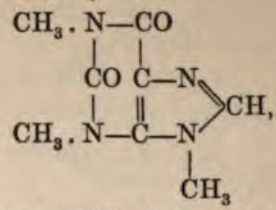
The diuretic action of this body is less marked than that of theobromine, but its action on the nervous system and heart is much more pronounced. On the heart the drug acts both locally and centrally. Probably the initial effect of a moderately large dose is to accelerate and weaken the beat (local action); later, the beat is slowed and its force increased (vagus action). Constriction, followed by dilatation, is the action on the blood vessels, and is also partly central and partly local. The vaso dilatation ceases to occur after a few doses. The diuresis is partly due to the effect of the drug on the parenchymatous renal cells, and is partly vasomotor. The action on the central nervous system is also partly a direct stimulation and partly the result of improved blood supply. Large doses raise the temperature.

Desoxycaffeine (1:3:7-trimethyl-2-oxy-1:6-dihydropurine),



acts in large doses like the corresponding theobromine compound in inhibiting diuresis, but it is more toxic, producing death with tetanic convulsions.

1:3:9-Trimethyl-xanthine,



is much less active than caffeine; it produces the same muscular rigidity, but more paralysis and less convulsions.

1:3:7:8-Tetramethyl-xanthine is very similar in its action to caffeine.

Two methyl compounds of the insoluble 6:8-dioxypurine are known, namely *iso*-caffeine or 1:7:9-trimethyl-6:8-dioxypurine, which has a much slighter action than caffeine, and 7:8-dimethyl-6:8-dioxypurine, which acts very slightly also, in a similar manner to theophylline.

E. Trioxy Derivatives.

The next oxypurine is 2:6:8-trioxypurine, or **uric acid,** which is inactive. But 1:3:7:9-tetra-methyl uric acid is active, and produces muscular rigidity, paralysis, and tetanic convulsions.

MODIFICATIONS OF SUBSTANCES OF XANTHINE TYPE.

Theobromine is a powerful diuretic, but its practical value is much diminished by the fact that it is only absorbed with difficulty. The formation of double salts which are easily soluble is achieved by means of the combination of this purine base with an alkali, thus:—

Diuretin is a compound of sodium theobromine with sodium salicylate containing 50 per cent. theobromine. The salicylate takes no part in the physiological effect.

Uropherin is a similar compound, lithium being substituted for sodium. This may possibly make the absorption somewhat more rapid, but otherwise has no advantage, as lithium is not inert and might even produce undesirable by-effects.

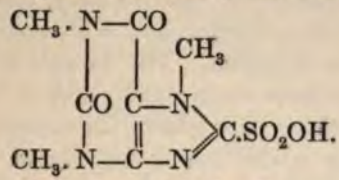
Agurin is sodium theobromine combined with sodium acetate.

Theobromine salicylate is an acid salt, and is also soluble in water.

Theocine sodium acetate is said to be somewhat safer than theocine, which has occasionally produced serious by-effects. It is a very powerful diuretic.

The attempts to produce caffeine derivatives of practical value have not been successful.

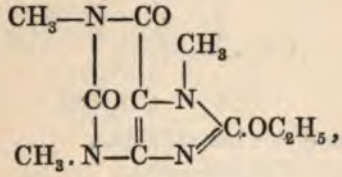
Sympherol is a sulphuric acid compound of caffeine,



Its salts are easily soluble, but with the disappearance of the action on the central nervous system the diuretic action vanishes also; moreover, they have a very bitter taste and are not stable.

Chloral and caffeine have been combined in the hope of neutralizing the stimulating action of the latter, but the drug so produced has no diuretic action and merely behaves like chloral hydrate.

Ethoxycaffeine,



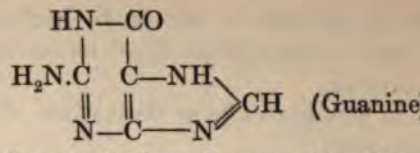
is diuretic, but also narcotic.

Methoxycaffeine is inactive.

The acyl-amino-caffeines are said to be powerful diuretics without any action on the central nervous system.

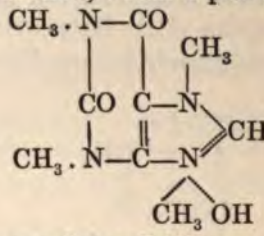
GENERAL REVIEW OF PURINE DERIVATIVES.

The introduction of methyl groups increases both the diuretic effect of the purines and also their action on voluntary muscle, whereas it decreases the action on the central nervous system and the general toxic effect. The introduction of oxygen alters the relative intensity of the various actions, but in no regular manner. The influence of a CO group seems to vary according as it is placed between NCH_3 or NH groups. As a general rule it produces a reduction in toxicity, but on the other hand guanine is less toxic than xanthine, though containing one CO group less—

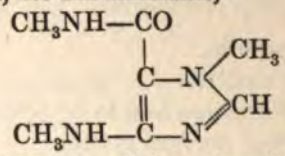

(Guanine)

The introduction of a hydroxyl group into the caffeine molecule reduces it to a physiologically inactive body, probably owing to the fact that it is thus converted into a substance which is easily decomposed in the organism. The formation of an ether with methyl or ethyl produces a compound which at first gives rise to no symptoms except those of a general intoxication. Subsequently, however, a rigidity resembling that produced by caffeine occurs. The action on the blood pressure is less marked than that of caffeine, but does not differ from it in quality. Medium doses in man are distinctly narcotic, but diuresis only occurs with fatal doses.

Caffeine-methyl-hydroxide, which is practically non-toxic,



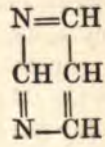
has no diuretic action, nor has caffeidine,



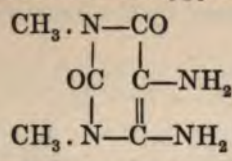
a decomposition product of caffeine, though this in large doses produces muscular rigidity and paralysis of central origin.

The diuretic action is, however, not attributable to the larger but to the smaller of the two rings of which the purine bodies are formed, and the same is true of the action on the muscles and central nervous system.

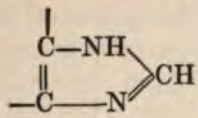
The pyrimidine compounds are derived from a nucleus formulated thus :—



1:3-dimethyl-4:5-diamino-2:6-dioxypyrimidine,



is inactive until the second (imidazol) ring is formed by linking the two nitrogen systems by the (CH) group, thus—

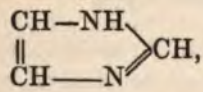


when theophylline results.

The introduction of chlorine, like that of hydroxyl, diminishes the action of caffeine, but the cyanogen group intensifies it.

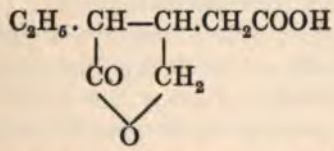
PILOCARPINE.

The imidazol or glyoxalin ring,

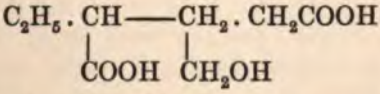


is common to the purine bodies and to pilocarpine; for which reason the latter body is described here.

This alkaloid, $C_{11}H_{16}N_2O_2$, gives on oxidation homopilopic acid, a substance represented in all probability by the structural formula—

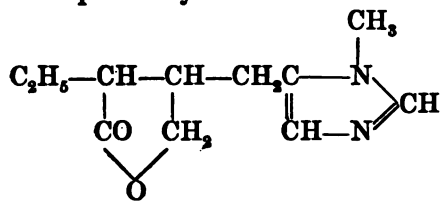


It is thought to act as a haptophore group. If the lactone structure of this derivative is destroyed by means of alkalis, the resulting substance,



is physiologically inert (Marshall). This seems generally true of

bodies with similar constitution. The alkaloid in all probability has a constitution expressed by the formula—



The part played by the glyoxolin portion in producing the characteristic effects of pilocarpine has not been determined.

Pilocarpine acts mainly in stimulating the nerve endings to secreting glands of all kinds. On the vagus fibres to the heart it acts in exactly the same way as electrical stimulation, through the 'nerve endings'. It stimulates all unstriped muscle in the same way, and lastly it acts on the post-ganglionic nerve fibres of the oculomotor nerve to the iris, producing myosis. It is thus the physiological antagonist of atropine.

It will thus be seen that, physiologically, pilocarpine acts very similarly to muscarine,

$$(CH_3)_3N\langle\begin{matrix}CH_2\\OH\end{matrix}\cdot CH(OH)_2,$$

and in a less accurate sense it resembles nicotine. Older determinations of the constitution of the alkaloid endeavoured to connect it with these two bodies, but recent investigations have shown that pilocarpine does not contain a pyridine nucleus.

Isopilocarpine is isomeric with pilocarpine and acts in the same way. It is six times weaker in efficient doses and at least twenty times weaker in large doses (Marshall).

Pilocarpidine, which differs from pilocarpine in possessing one CH_3 group less, is still weaker than pilocarpine.

Jaborine is apparently a condensation product of two molecules of pilocarpine. It possesses an atropine-like action.

CHAPTER XII

THE ALKALOIDS. Chemical and physiological introduction. Method of classification. General principles of Alkaloidal action. The Pyridine group—Coniine, Nicotine, and allied substances.

THE ALKALOIDS.

THE vegetable alkaloids are a group of substances, nearly all tertiary amines, which are specially abundant in the dicotyledons. It is seldom that one alkaloid only is present, as a rule there are many, and they generally occur combined with the so-called plant acids—citric, malic, and tannic, although a considerable number are found associated with peculiar acids; the quinine alkaloids, for instance, with quinic acid, the opium group with meconic acid, and the aconitine with aconitic acid. The discovery of pyridine in 1846 by Anderson and of quinoline in the previous year by Runge, together with the elucidation of the constitution of these substances, was the first great step in the investigation of the alkaloids. Gerhardt had found in 1842 that strychnine, cinconine, and quinine heated with potash gave quinoline, whereas nicotine, coniine, brucine, and others heated with zinc dust gave either pyridine or its homologues. The alkaloids, then, appear to be derived from pyridine and quinoline in the same way that the aromatic substances are derived from benzene. With the exception of pilocarpine, caffeine, and theobromine, which have been described under the purine derivatives, this class of organic derivatives may be defined as products of plant life derived from those two substances or from nuclei closely related to them.

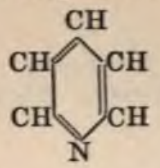
Before discussing the physiological properties of the group, a short account of the chemistry of these ring complexes will be given.

I. PYRIDINE AND PIPERIDINE.

Pyridine, C_5H_5N, and many of its homologues can be obtained from bone oil, and are also found in coal tar.

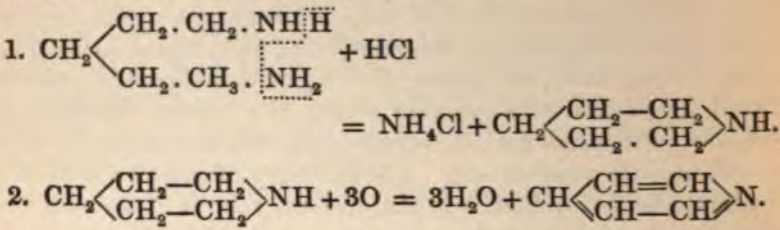
Pyridine itself shows great stability towards oxidizing agents, but its homologues behave in a similar manner to those of benzene, being converted on oxidation into acids which still contain the pyridine nucleus.

As in the case of the aromatic derivatives, this behaviour is assumed to be due to the presence of a six-membered ring containing one nitrogen atom—



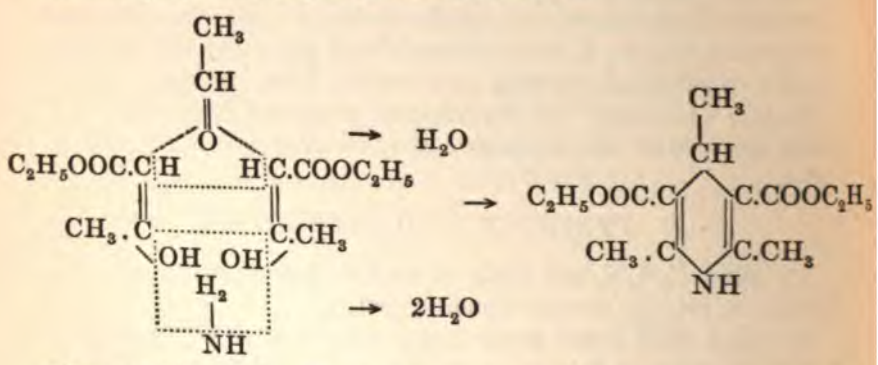
or, as it will be written in the following pages

The formation of pyridine from pentamethylenediamine by heating the hydrochloride, and the oxidation of the resulting piperidine is in agreement with this conception:—



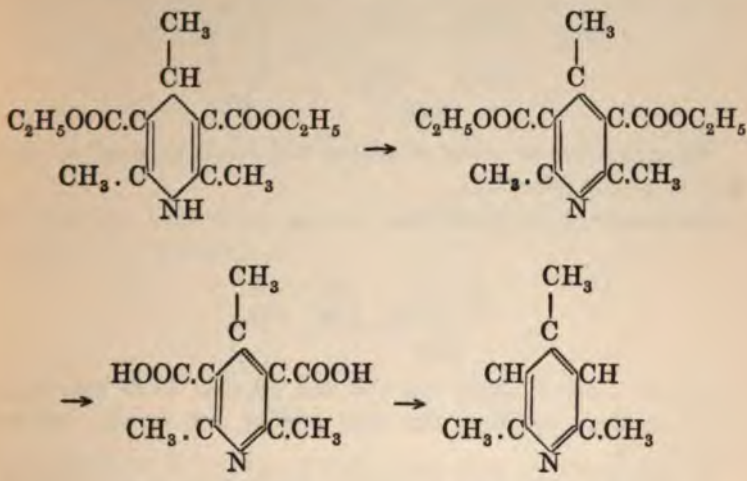
One method used in the synthetic formation of pyridine derivatives is due to Hantzch, and consists in the condensation of β-keto compounds (such as acetoacetic ester) with aldehydes and ammonia.

An example of this condensation is seen in the following formation of dihydro-collidine-dicarboxylic ester by the interaction of acetaldehyde, ammonia, and acetoacetic ester—

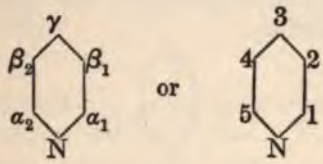


On oxidation, the dihydro derivative yields the corresponding pyridine substitution product, which on saponification gives the

di-carboxylic acid. On heating with lime the carboxyl groups are eliminated and $\alpha_1\alpha_2\gamma$-trimethyl-pyridine results—

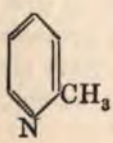


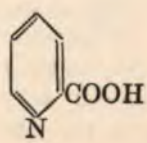
The nomenclature of the pyridine derivatives will be clear from the following diagram. The first system will be adopted in this work:—



The pyridine bases are colourless liquids with a peculiar odour; they are tertiary amines and form crystalline salts with one equivalent of acid.

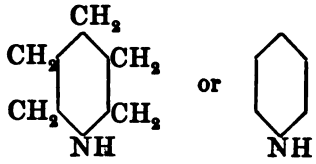
Oxidizing agents do not, as a rule, attack pyridine itself, but its homologues, even phenyl pyridine, are converted into pyridine-carboxylic acids. Thus—

α-Methyl-pyridine 

gives 

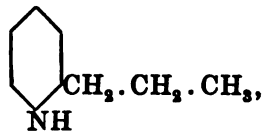
α-pyridine-carboxylic acid.

Reducing agents convert pyridine or its derivatives into hexa-hydro-pyridine or piperidine,



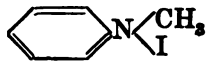
Piperidine has an odour of pepper and occurs as a salt of piperic acid in pepper (piperine).

Coniine, α-propyl-piperidine,

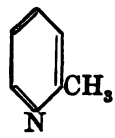


found in hemlock seeds, was the first alkaloid to be synthesized. Starting from pyridine, this was carried out in the following manner:—

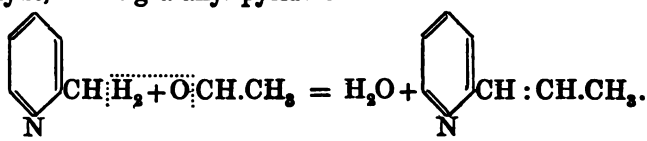
1. Pyridine acted upon by methyl iodide gives an iodomethylate,



and when this substance is heated to 300° C. it undergoes an intra-molecular change, characteristic of this type of derivative, and gives α-methyl-pyridine,



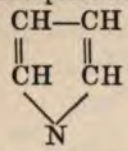
2. α-Methyl-pyridine condenses at high temperature with paraldehyde, forming α-allyl-pyridine—



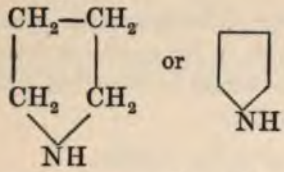
3. α-Allyl-pyridine on reduction gives α-propyl-piperidine, but the resulting substance is optically inactive, whereas coniine is *dextro*-rotatory. When the synthetic substance is crystallized with *dextro*-tartaric acid, *dextro*-coniine-tartrate separates out first; and if this is decomposed with potash, coniine, identical with the natural product, is formed.

II. PYRROL AND PYRROLIDINE.

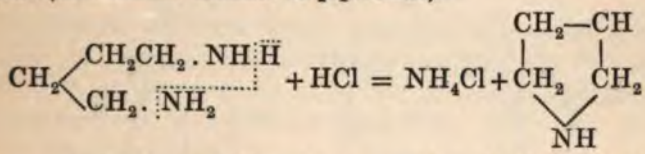
Pyrrol, C_4H_5N, is a feebly basic body found in coal tar and bone oil, containing a four-membered carbon chain united by the imide group; its structure is represented by the formula—



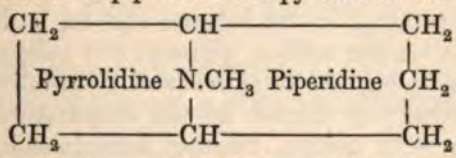
On reduction with hydriodic acid and phosphorus, it gives tetrahydropyrrol or pyrrolidine,



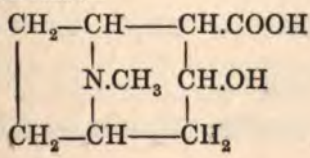
This substance is a much stronger base than pyrrol, and may be obtained from penta-methylene-diamine by heating its hydrochloride (in a similar manner to piperidine)—



From *n*-methyl-pyrrolidine a large number of different alkaloids of the atropine-cocaine group are derived. They are substitution products of a combined piperidine and pyrrolidine nucleus—

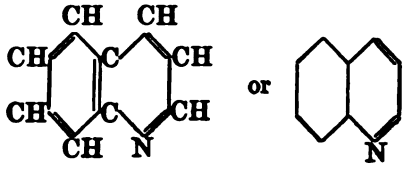


Ecgonine, for instance, which is formed by the action of concentrated mineral acids or baryta water, on cocaine, has the following constitutional formula:—



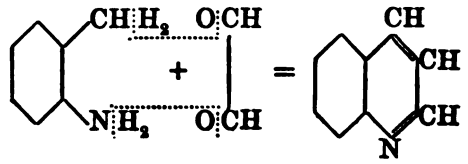
III. QUINOLINE.

The quinoline bases occur with pyridine in bone oil, and their method of synthesis and decomposition all point to the constitutional formula—

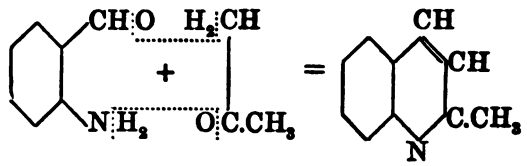


That is, a combination of benzene and pyridine nuclei. This is well shown, for instance, in its synthesis from (A) *o*-toluidine and glyoxal, (B) or the production of *α*-methyl-quinoline from *o*-amido-benzaldehyde and acetone:—

A.



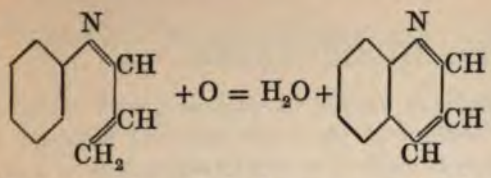
B.



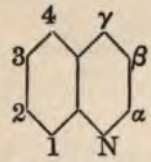
One general method for the formation of quinoline and its derivatives, substituted in the benzene nucleus, is due to Skraup, and consists in heating aniline, glycerin, and sulphuric acid with some oxidizing agent, such as arsenic acid or nitrobenzene. In all probability acrolein is formed by the dehydration of glycerin; this combines with aniline, forming acrolein-aniline, which is then oxidized to quinoline:—

1. $$\begin{matrix} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{matrix} - 2H_2O = \begin{matrix} CH_2 \\ \| \\ CH \\ | \\ CHO \end{matrix}$$

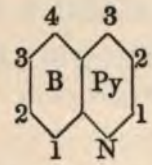
2. $C_6H_5N\!:\!H_2 + O\!:\!HC.CH:CH_2 = H_2O + C_6H_5N:CH.CH:CH_2$

3. 

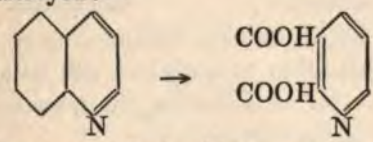
The three replaceable hydrogen atoms in the pyridine nucleus of quinoline are designated by α, β, γ, those of the benzene nucleus with 1, 2, 3, 4.



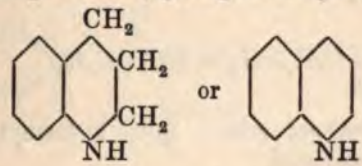
Another method consists in numbering the former Py 1, 2, 3 and the latter B 1–4.



The quinoline bases are liquids possessing a penetrating odour, and, like the pyridines, are tertiary bases. They are but slightly attacked by nitric or chromic acids, but are oxidized by potassium permanganate to α-β-pyridine-dicarboxylic acids, the benzene nucleus being destroyed:—



On reduction with zinc and hydrochloric acid, the pyridine nucleus takes up four hydrogen atoms, giving tetra-hydro-quinoline,



A considerable change in chemical characteristics follows this reduction, since the resulting substance behaves like a secondary fatty amine attached to an aromatic nucleus.

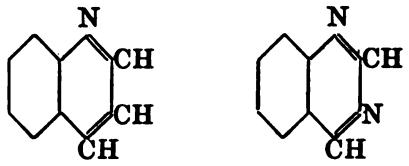
IV. ISO-QUINOLINE.

iso-Quinoline, C_9H_7N, is similar to quinoline, with which it is isomeric; it occurs with it in the crude material obtained from coal tar. On oxidation it yields β-γ-pyridine-dicarboxylic acid, and for this reason and others the following formula has been assigned to it:—

On reduction, it gives a powerful base, tetra-hydro-*iso*-quinoline.

IV (A). QUINAZOLINE DERIVATIVES.

Quinazoline may be regarded as quinoline, in which a (CH) group is replaced by a second nitrogen atom in the 1:3 position to the one already present.



Quinoline. Quinazoline.

The dihydro derivative of this substance is of interest, and, on account of its relationship to quinoline, will be alluded to in this place, although, as far as is known, the quinazoline nucleus does not appear in any of the alkaloids.

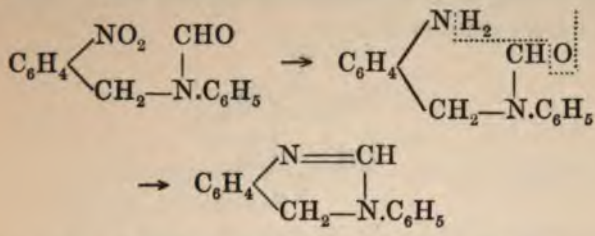
When *o*-nitro-benzylchloride is acted upon by aniline the following reaction takes place:—

$$C_6H_4\begin{cases}NO_2\\CH_2Cl\end{cases} + C_6H_5NH_2 = HCl + C_6H_4\begin{cases}NO_2\\CH_2 . NHC_6H_5.\end{cases}$$

The resulting substance readily gives a formyl derivative when acted upon by formic acid.

$$C_6H_4\begin{cases}NO_2\\CH_2 . NHC_6H_5\end{cases} + H.COOH = H_2O + C_6H_4\begin{cases}NO_2 & CHO\\ & |\\CH_2 . & N.C_6H_5\end{cases}$$

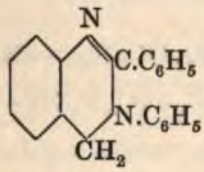
On reduction the formyl compound gives phenyl-dihydro-quinazoline—



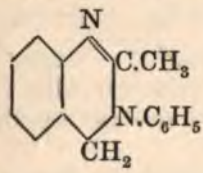
This derivative of dihydro-quinazoline was expected to possess antipyretic properties, but was found to have only slight toxic action and to give rise to a subjective feeling of hunger. It was introduced into pharmacy, either as a free base or as the hydrochloride, under the name of **Orexine,** but owing to the objectionable taste of these substances they have been replaced by the tannate, a chalky, white, odourless and tasteless powder, readily soluble in dilute hydrochloric acid and hence also in the gastric juice, but, like the base itself, insoluble in water.

It is said to aid digestion and to increase the secretion of hydrochloric acid in the stomach; it has, however, in some cases proved too irritating to the gastric mucosa, and unless well diluted may produce vomiting.

Diphenyl-dihydro-quinazoline



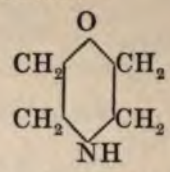
has no action, whereas the methyl derivative



is a very toxic substance.

V. MORPHOLINE AND PHENANTHRENE.

A. Knorr designated as morpholine the base whose constitutional formula is represented as follows :—



This compound is extremely interesting, owing to its relationship to the opium alkaloids. The objections to the old method of preparation from diethanol-amine and sulphuric acid are the difficulties experienced in obtaining the amine and also its high price.

$$NH\langle\begin{matrix}CH_2\cdot CH_2\cdot OH\\CH_2\cdot CH_2\cdot OH\end{matrix}\rangle \rightarrow H_2O + NH\langle\begin{matrix}CH_2\cdot CH_2\\CH_2\cdot CH_2\end{matrix}\rangle O.$$

In 1901, however, Marckwald and Chain found that it could be easily obtained by the following reactions :—

1. $C_6H_4\langle\begin{matrix}CH_3\\SO_2NH_2\end{matrix}$ + $2BrCH_2\cdot CH_2\cdot OC_{10}H_7$ + $2KOH$

o-Toluene sulphamide. Brom-ethyl-β-naphthyl ether.

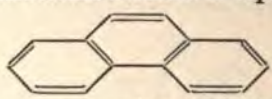
$$= C_6H_4\langle\begin{matrix}CH_3\\SO_2N(CH_2\cdot CH_2\cdot OC_{10}H_7)_2\end{matrix} + 2KBr + 2H_2O$$

2. This derivative is quantitatively decomposed by mineral acids into toluene, sulphuric acid, β-naphthol, and morpholine.

$$C_6H_4\langle\begin{matrix}CH_3\\SO_2\cdot N(CH_2\cdot CH_2\cdot OC_{10}H_7)_2\end{matrix} + 3H_2O$$

$$= C_6H_5CH_3 + H_2SO_4 + 2C_{10}H_7OH + NH\langle\begin{matrix}CH_2\cdot CH_2\\CH_2\cdot CH_2\end{matrix}\rangle O$$

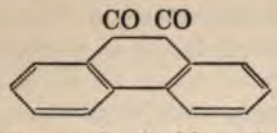
B. Phenanthrene, $C_{14}H_{10}$, occurs, together with anthracene, in coal-tar, and its constitutional formula is represented as follows :—



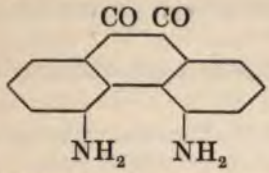
Owing to its intimate connexion with the opium alkaloids, the study of its derivatives has received considerable attention during the last few years.

Pschorr and his students have devised new methods for its synthesis; Werner and Schmidt have investigated the sulphonic acids and their decomposition products, the nitro and amido compounds, and also the derivatives of phenanthraquinone.

Phenanthraquinone is obtained by the oxidation of the hydrocarbon in glacial acetic acid with chromic acid, and has the following constitution: —



The 4:5-dinitro compound of this quinone readily gives the corresponding diamido derivative,



from which bodies closely related to morphine can be obtained.

GENERAL PHYSIOLOGICAL CHARACTERISTICS OF THE ALKALOIDS.

Of the large number of bodies of an alkaloidal nature known, a fair proportion are constantly administered as therapeutic agents. Of these, however, by far the greater number are given in a mixed form; that is, in official tinctures and extracts which contain the total alkaloids to be obtained from any given plant. The practical therapist is therefore, as a rule, in ignorance as to the physiological effect of the majority of the substances with which he is dealing, a matter which would perhaps trouble him more were it not for the fact that in most cases these substances are present in very small quantities, and are thus to all intents and purposes inactive. When we exclude those 'less important' alkaloids the physiological bearing of which has not been exhaustively studied, the list becomes notably diminished in length; perhaps there are some thirty or forty bodies of such primary importance pharmacologically that a more or less complete determination has been made of their action on living organisms. But to only a few of these has it hitherto been possible to assign a definite chemical position. Some are of doubtful purity, many are only known by their empirical formula, and thus for our present purposes there remains hardly a score of substances which can profitably be discussed. These are classified from the

chemical standpoint into five or six groups, according to the character of the nitrogen-bearing ring from which they are derived, and the various members of the different groups exhibit a certain rough resemblance to each other in their physiological action. The groups, the parent substances of which have been previously described, are :—

I. **The Pyridine group,** containing coniine, nicotine.

II. **The Pyrrolidine group,** containing cocaine, atropine, hyoscyamine.

III. **The Quinoline group,** containing quinine, cinchonine, strychnine, brucine.

IV. **The** *iso*-**Quinoline group,** containing hydrastine, narcotine, cotarnine, berberine.

V. **The Morpholine** (?)-**Phenanthrene group,** containing the opium alkaloids, morphine, codeine, thebaine.

In the first group are contained substances which act mainly on the peripheral nervous system, though central effects are also to be obtained.

In the second group certain somewhat specialized actions are observed, mainly on sensory nerve endings, but here also large doses have an effect on the central nervous system, especially the higher cerebral centres.

The third group contains substances powerfully toxic for living protoplasm; they have a certain preferential action on the nerve cells in the spinal cord, which is more marked in some members of the group than others; they have very little, if any peripheral action.

In the fourth group are a number of bodies which do not entirely differ in their action from those of the third and fifth groups; they have a central action mainly on the medulla, but to some extent are also muscle poisons.

In the fifth group central action again predominates, and in man this action is especially noticeable, owing to the high degree of development which the cerebral centres attain. The members of this group have also an action on the cord resembling that of some members of the fourth group.

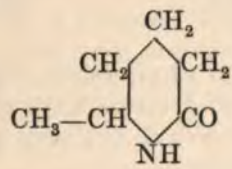
The production of a large number of artificial alkaloids, differing in various directions from those natural alkaloids the chemical constitution of which is determined, has thrown considerable light on various factors in the physiological action of these bodies. Thus the position of the substituting groups may be altered; their

constitution varied in many ways, or they may be removed altogether. As a rule, the main physiological action of an alkaloid can only be altered or destroyed by profound alterations in the atom-groups which constitute the central ring or 'nucleus' of the molecule. The functions of the substituents appear to be mostly 'haptophore'; that is, they enable the central groups to combine with the protoplasm of certain cells and thus to produce their proper effect. If they are removed or so modified as to entirely destroy their haptophoric power, the pharmacological action of the drug will be correspondingly altered. But on replacing or restoring the haptophoric group, the original characteristics will return, as the central nucleus has remained all the while intact. Thus the phenol-hydroxyl group in morphine seems necessary for the manifestation of the narcotic action, forif the hydrogen is replaced by acid or alkyl radicals this effect can no longer be obtained (p. 293); on the other hand, the well-known physiological differences between morphine and apomorphine are due to correspondingly radical changes in the central part of the molecule (p. 301).

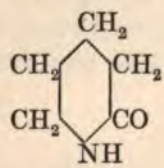
If the side-chain is extended to a great extent, the physiological action of the ring may be lost, and the effect of the alkyl portion of the molecule become preponderatingly obvious. An example of this may be found (p. 251) in the pyridine compounds.

An example, too, of the effect of alkyl substituents is well seen in the α-keto-piperidine series (or *iso*-oximes).

α-Oxy-α-pipecoline

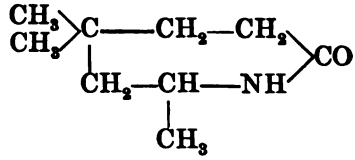


is more active than piperidon—



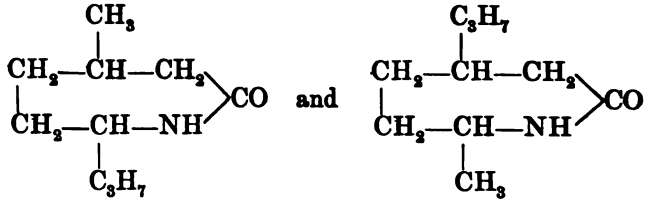
β-methyl-hexanone-*iso*-oxime is five times as active as the α compound (experiments on mice).

Trimethyl-heptanone-*iso*-oxime



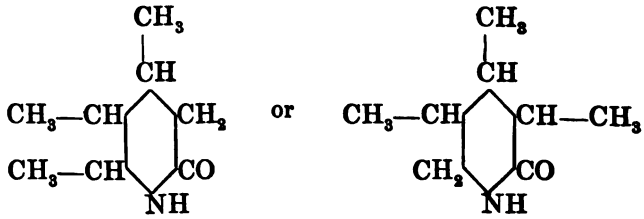
is much more toxic than hexanone-*iso*-oxime, and acts more powerfully on the motor nerve endings.

The two isomers of methyl-propyl-heptanone-*iso*-oxime, namely,



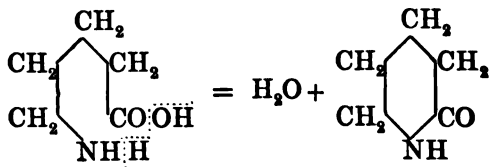
act very similarly to one another, and differ from the parent base in producing less convulsive effect and more narcosis; they are also more powerful in the paralytic action on the motor nerve endings.

Trimethyl-*iso*-propyl-piperidon

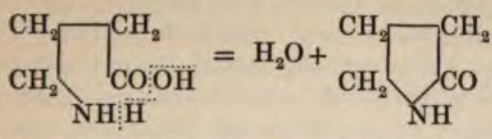


is ten times as poisonous as piperidon; the alkyl groups suppress the convulsive action and accentuate the paralyzing action on the motor nerve endings, which is not very marked even with fatal doses of the parent substance.

Certain points as to the structure of the central ring are also of importance. If the ring itself is broken, the physiological action is lost. Examples of this may be seen in δ-amido-valerianic acid, which by the loss of water gives piperidon



and δ-γ-Amido-butyric acid and α-pyrrolidon,



The two bodies in which the ring is not closed, are without any marked action, whereas the closed-ring derivatives formed from them by loss of the elements of water act like strychnine (or perhaps picrotoxin).

Similarly, pentamethylene-diamine

$$CH_2\begin{matrix}CH_2 . CH_2 . NH_2\\ CH_2 . CH_2 . NH_2\end{matrix}$$

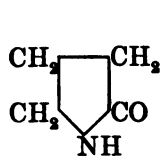
is not toxic, whereas the closed-chain derivative, piperidine, formed from it by loss of ammonia (see p. 234), has a definite toxic action. Metanicotine, which has only one-tenth the toxic power of nicotine, may also be cited as an example (p. 256).

The number of groups in the ring influences the activity of the compound, but does not produce any alteration in kind. Piperidine, a six-membered ring, is more toxic than pyrollidine with five. The position of the N atom in the double benzene-pyridine ring does not appear to be of importance, thus quinoline and *iso*-quinoline are physiologically identical.

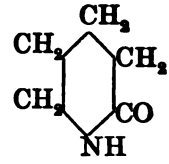
On the other hand, the replacement of a CH group in benzene by nitrogen causes a marked difference in the action of the resulting compound and its derivatives. Thus bases derived from the benzene ring alone, aniline for example, are characterized by their power of reducing the body temperature and breaking up the red blood cells, whereas pyridine has neither antiseptic nor antipyretic power. The condensation of a benzene and pyridine ring (quinoline) results in powerfully toxic and antiseptic bodies, but the double benzene nuclei, diphenyl, phenanthrene, and naphthalene, have no antipyretic derivatives. The condensation of two rings of the pyridine series (dipyridine, parapicoline, &c.) gives rise to bodies resembling in their action the natural alkaloids, to which they are chemically related.

Some idea of the variations in action which are conditioned by changes in ring-structure may be gained from a study of the artificial ring compounds—the cyclic isoximes, such as piperidon,

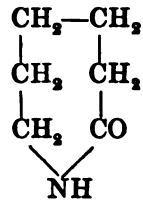
ketones, such as cyclohexanone, and imines, piperidine. The first all contain the group (CO.NH) in the ring; they are the least toxic of the three series, and have least paralysing action on the motor nerve endings and the central nervous system. They are characterized by producing picrotoxin-like convulsions, i. e. convulsions dependent on excitation of bulbar and possibly cortical centres, unaccompanied by increased reflex irritability. The lower members of the series are the least active, in the higher members the picrotoxin effects are most marked.



Pyrrolidon.

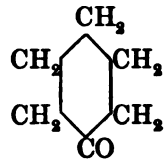


Piperidon.



Hexanonisoxime.

The ketones,



more toxic, produce more paralysis of central origin, but no convulsions; the imines are the most toxic of all, and have most action on the motor nerve endings. In all three series the larger rings are the more active.

The variation in the selective action of these compounds necessarily implies variation in the protoplasm of the different structures in the body on which they act, a matter which has already been considered (p. 19). From this point of view the alkaloids may be regarded as a number of keys, each of which will fit into certain protoplasmic locks, but it must also be admitted that the locks are often very bad ones, as in many instances differently shaped keys will turn them. Thus, in general, chloroform, morphine, quinine,

and aconitine, lower the body temperature, whilst strychnine, nicotine, picrotoxin, caffeine, and cocaine raise it—a very miscellaneous list from the structural point of view—and later on abundant examples will be seen under such well-defined actions as local anaesthesia and mydriasis (p. 260).

The alkaloids are classed by Loew as special poisons, that is, those which do not in sufficiently strong dilution invariably destroy protoplasm. They act only on certain kinds of protoplasm, e. g. that of the central nervous system, but do not damage other kinds (see p. 17). The toxic action is merely an exaggeration of the pharmacological action of the alkaloids when used as drugs, the dosage being so regulated that stimulation and not destruction is produced in the cell bodies. It may, of course, happen that with smaller doses the toxic action of the drug entirely disappears, owing to the dilution being too great to affect those structures on the disturbance of which the fatal issue depends. For instance, quinine, when given in large enough doses to destroy the malarial parasite, does not necessarily produce its specific effect on the cerebrum.

We shall now proceed to consider the various alkaloids of which the chemical structure is known, adopting the classification previously mentioned. For practical convenience, the opium alkaloids which belong chemically to two groups have been considered together. Hordenine is separately described (see p. 303).

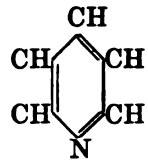
In order not to interrupt unduly the arrangement of the alkaloids on a chemical basis, a chapter has been added in which the various synthetic substitution products recently introduced into practice are described. These, though pharmacologically similar to the alkaloids they are intended to replace, are often very different chemically, and hence it was thought advisable to deal with them separately in a chapter supplementary to the systematic account of the alkaloidal bases.

I. THE PYRIDINE GROUP.

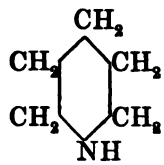
The principal alkaloids to be considered in this group are coniine and its stereoisomer, methylconiine, conhydrine and its isomer pseudo-conhydrine (derived from hemlock), nicotine and nicoteine (from tobacco), and piperine (from black pepper).

Physiologically and chemically these bodies vary considerably in complexity, and it will be well to begin with the simplest, namely that substance forming the chemical basis of that group, pyridine.

This, containing as it does one atom of tertiary nitrogen in the ring, is very inactive;

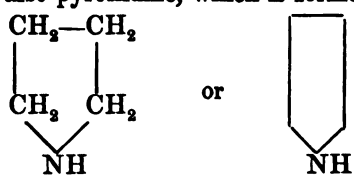


hydration, which results in the formation of an imide group, produces the much more active body, piperidine,

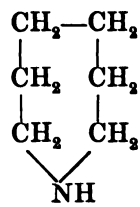


Pyridine, which is a liquid with a powerful and distinctive odour, if inhaled, stimulates the fifth nerve and produces dyspnoea, then slow, shallow breathing, and eventually sleep. In very large doses it paralyses the sensorium, producing complete anaesthesia and abolition of reflexes, smaller doses may inhibit respiration; on stimulation of the vagus centre in dogs breathing stops in expiration. Small doses act on the heart, increasing the force and slowing the rhythm of the beat; large doses paralyse the muscle, causing a fall of blood pressure, and finally stop the heart altogether. Doses of 1 gram (15 minims) per diem produce no symptoms.

Piperidine, and also pyrollidine, which is formulated—



and cyclohexamethylene-imine



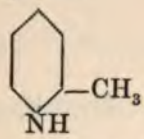
have much the same action, producing in cold-blooded animals

a rise of blood pressure and general paralysis of central origin.[1] Large doses inhibit the heart.

The introduction of alkyl side-chains into the pyridine ring, resulting in the formation of such substances as ethyl-pyridine (lutidine), α-propyl-pyridine (collidine), has much the same effect as the addition of hydrogen atoms, and with the length of the side-chains the original pyridine action disappears, and an intoxicating effect on the higher cerebral centres becomes apparent. There is no difference in kind between compounds in which the side-chain is attached to a carbon atom and those in which the alkyl groups replace the imido-hydrogen atom in the reduced piperidine.

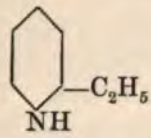
If both these methods are combined, and alkyl side-chains are added to a hydrated pyridine ring, a series of bodies more powerful than piperidine, but acting in a similar manner, is produced.

Pipecoline is α-methyl-piperidine



and resembles curare in its action. It does not inhibit the heart.

Ethyl-piperidine



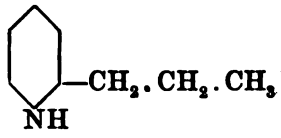
acts similarly in smaller doses.

The addition of higher alkyls to the piperidine ring increases the toxicity of the resulting compounds; and though the added atom groups increase in arithmetical progression, the toxicity increases to a much greater degree, approximately in geometrical progression.

The higher members of the series approach in their physiological action the lower members of the quinoline series, but the lethal doses of the former are only about half the size, and there is more tendency to death from respiratory failure.

[1] Some authorities state that the action of piperidine is on the motor nerve endings and that it has no central paralysing effect.

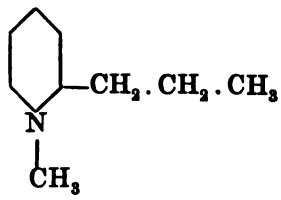
Coniine is propyl-piperidine—



It is more powerful still, though similar in its action to piperidine. It acts probably mainly on motor nerve endings, producing muscular paralysis. It also raises the blood pressure, by local action on the peripheral vessels, and slows the pulse by action on the vagus centre or terminations; there is also slight quickening of respiration, followed by retardation, an effect probably partly central and partly peripheral. *iso*-Propyl-piperidine has a similar action to coniine, but it has only one-third of the toxicity of that substance.

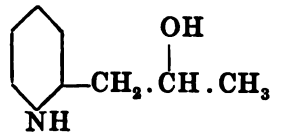
iso-Coniine apparently acts like coniine.

***n*-Methyl-coniine**—



The imide hydrogen of coniine in this compound is now replaced by a methyl group; no great physiological change, however, occurs. Dimethyl-coniine is much less toxic. The muscular spasms occurring after coniine poisoning are said by some authors to be absent after methyl-coniine, which also acts more specifically on the spinal cord. Its fatal dose is one-third less than that of coniine.

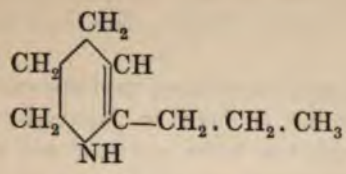
Conhydrine



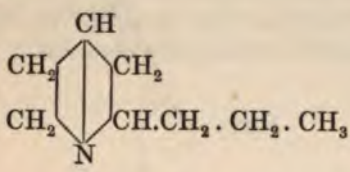
and its isomer, pseudo-conhydrine, act less powerfully than coniine, the proportional doses being ·03, ·2, and over ·3 grams per kilogram body-weight in guinea-pigs (Findlay).

A series of bodies known as **Coniceines**, having two atoms of hydrogen less than coniine, are of interest, as they are thought to illustrate the action of the double bond (see p. 50).

γ-Coniceine

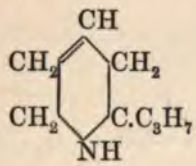


is said to be seventeen times more toxic than coniine; and α-coniceine, the constitution of which is uncertain, is also more toxic; it may be a stereo-isomer of δ- and ε-coniceine. δ-Coniceine, which may be formulated—



is less active, owing possibly to the presence of a tertiary nitrogen atom.

β-Coniceine, which has probably the structural formula—



is less toxic than α-coniceine. The latter is more toxic than coniine.

Pipecoline and ethyl-piperidine have been previously mentioned (see p. 251). The piperidine homologues of the composition $C_7H_{15}N$, that is di-methyl piperidine and ethyl-piperidine, are termed lupetidines, whereas the methyl-ethyl derivatives are called copellidines. These substances are formed by the reduction of the corresponding homologous pyridines with sodium and alcohol.

The toxicity of these compounds increases approximately in geometrical progression, as their molecular weight increases in arithmetical progression. This holds good, however, only up to the *iso*-butyl and hexyl derivatives, which both show a marked decrease in toxicity. The proportions are 1 : 2 : 4 : 8 : 5 : 4.

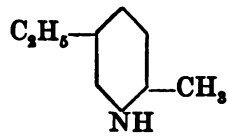
Lupetidine (α-α′-dimethyl-piperidine) acts like curare; it has no special cardiac action, but paralyses respiration. It has a toxic

action on the red blood cells, producing vacuolation; the central nervous system is slightly affected, and there is some local anaesthetic action.

β-Ethyl-piperidine (β-lupetidine) produces salivation and tetanic convulsions. It is not so toxic as β-propyl-piperidine, which it otherwise resembles; the latter, again, is not so toxic as coniine. Propyl-lupetidine, the most powerful poison of this series, in addition to its action on the motor nerve endings, has a marked effect on the central nervous system, but does not damage the red blood cells so much as the other members of the series.

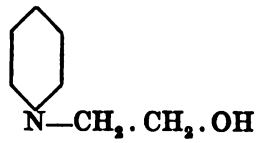
iso-Butyl-lupetidine paralyses the heart and has a true narcotic action; it also paralyses the motor nerve endings. In hexyl-lupetidine this effect is but slightly observed.

Copellidine

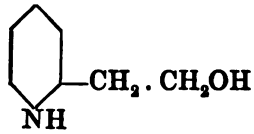


is twice as toxic as lupetidine, and acts principally on the motor nerve endings.

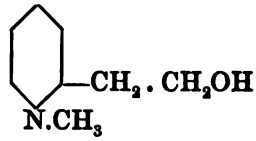
Piperylalkin,



Pipecolylalkin,



and methyl-pipecolylalkin,

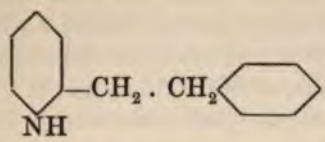


have been physiologically investigated. The first two produce paralysis of central origin, the last appears to be innocuous.

From a consideration of these compounds it will be seen that not only the size but also the position of the side-chain in relation to

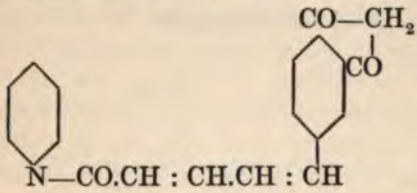
the N in the ring may influence physiological action—asymmetrical compounds do not behave quite similarly to the symmetrical. As a rule, too, though not always, the alkaloids in which the substituents are attached to nitrogen are more active than those in which the groups are linked to carbon.

Stilbazoline



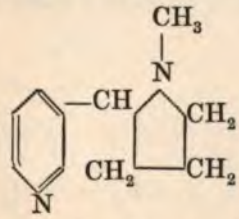
has little power of exciting convulsions, but is powerfully paralysing. The fatal dose is about three times as large as that of coniine.

Piperine, which has a structural formula represented by

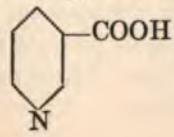


acts similarly to piperidine, but has less action in contracting the peripheral arterioles. This appears to be due to the attachment of the acid radical to the nitrogen instead of one of the carbon atoms in the ring.

Nicotine has a somewhat more complicated molecular structure, and in all probability is α-pyridyl-β-tetrahydro-*n*-methyl-pyrrol; it may be represented by the following formula:—



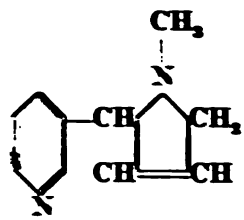
On oxidation it gives rise to β-pyridine-carboxylic acid,



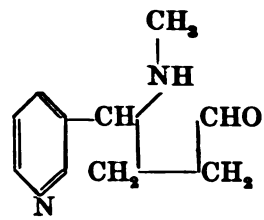
and is consequently a β-derivative of pyridine; starting from β-amido-pyridine, Pictet and Crepieux have synthesized a base showing all the properties of the natural alkaloid.

The action of nicotine closely resembles that of coniine, but it is more powerful. If given in doses not large enough to be immediately fatal, nicotine causes clonic and tonic convulsions of central origin, stimulation of the respiratory centre, a rise followed by a fall of arterial blood pressure, and finally extreme depression of the whole central nervous system, which ends in death. Nerve cells in the peripheral ganglia are paralysed, hence after preliminary stimulation there is diminution in the secretory activity of glands. Small doses slow the heart, larger doses render its action rapid and irregular. This is partly vagal and partly due to direct action on the musculature. The action on the blood vessels is peripheral, and differs from that of adrenalin in that it lasts for a shorter time, and is followed by a period of vaso-dilatation.

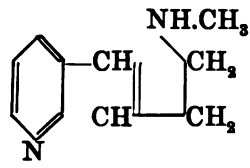
Nicotine



has a similar but more powerful action than nicotine, apparently traceable to the presence of the double bond, whereas **oxynicotine**, obtained by the action of hydrogen peroxide on nicotine, is weaker. Its constitution is that of an aldehyde, and in its formation the pyrrolidine ring is probably broken—



Metanicotine, which acts like nicotine, is much weaker. A dose nine times as large is required to produce the toxic symptoms, and is only fatal in double the time. The constitution of metanicotine is represented by the formula—



and it is consequently methyl-β-pyridyl-δ-butyl-amine. Thus in these two compounds the original physiological action remains, though the pyrrolidine ring is destroyed. This shows that the ring formation is not essential for the production of the pyrrolidine action.

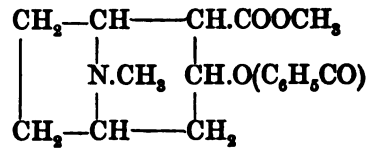
The physiological effects of all these bodies are very similar, from pyridine onwards, but they differ markedly in degree. The most curious point of difference is that pyridine itself lowers the arterial pressure by weakening the heart, whereas all the rest, which are hydrated bodies, raise the arterial pressure by constricting the smaller arteries. The marked action which nicotine has in this respect may be due not only to the presence of the pyrrolidine ring, but also to some synergetic action from the pyridine, which is latent in that compound and requires the presence of extra hydrogen atoms, or of some substituent group to give it actuality.

CHAPTER XIII

THE ALKALOIDS (CONTINUED).—Pyrrolidine group—Cocaine, Atropine, Hyoscyamine. Quinoline group—Quinine, Cinchonine, and their substitutes. Strychnine and Brucine.

II. THE PYRROLIDINE GROUP.

The constitution of **Cocaine** is expressed by the formula—



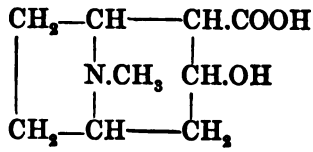
and is thus benzoyl-ecgonine-methyl-ester, the two hydrogen atoms in the carboxyl and hydroxyl groups having been replaced by methyl and benzoyl respectively.

The chief physiological properties of cocaine are:—

1. It stimulates the vaso-motor centre and partially paralyses the vagus. It also acts slightly as a stimulant to the accelerator nerves to the heart. For these reasons the blood pressure is raised.
2. Its action on the cerebral and spino-medullary centres is at first excitant and then profoundly depressant. It thus causes death by convulsions or paralysis of the respiratory centre.
3. It causes peculiar 'foam-like' degeneration and vacuolation of the liver cells, which Ehrlich says is quite characteristic in mice.
4. It raises the body temperature.
5. It dilates the pupil.
6. It increases power of muscular work.
7. It produces local anaesthesia.

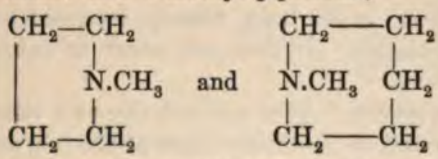
Cocaine thus differs remarkably from its immediate chemical predecessor, ecgonine, in its physiological action.

This substance



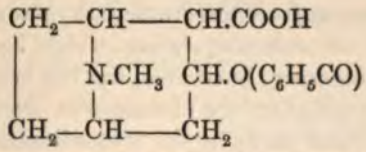
is not a very powerful poison. Its main action is to cause degeneration of the liver cells; in large doses it causes paralysis and death. The former property (common to all ecgonine derivatives) it transmits to cocaine; it appears to depend on the presence of the tertiary nitrogen atom, for if methyl iodide, CH_3I, is added to the ($N.CH_3$) group, and an ammonium compound is formed, no liver degeneration occurs.

Ecgonine owes its feeble action partly to the presence of the carboxyl group, which affords no anchoring facility for the molecule to the protoplasmic substance, and is with difficulty broken up in the organism. Ecgonine itself is derived from two single rings, *n*-methyl-pyrrolidine and *n*-methyl-piperidine,

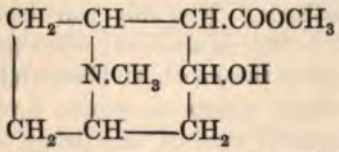


substances having similar physiological actions. They raise the blood pressure, depress the peripheral cardiac inhibitory mechanism, and cause general paralysis of central origin. These actions, lost in ecgonine, reappear in cocaine, owing to the substitution of the alkyl radical for the hydrogen in the carboxyl group.

Benzoyl-ecgonine



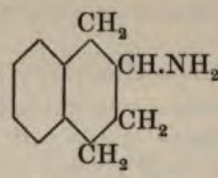
is twenty times less powerful a poison than cocaine, owing to the presence of the COOH group; its action, moreover, differs from that of cocaine, and resembles that of curare. Whatever action it has seems due to the presence of the benzoyl group; where this is absent, as in ecgonine-methyl-ester,



a similar diminution of toxicity occurs. Thus there are two groups of physiological effects, firstly, the one which may be called the generally toxic action, and secondly, the action on the liver cells,

both of which are correlated to the chemical structure of the molecule. The remaining groups will now be considered.

4. Elevation of Temperature. This is quite a marked property, and the only substance which exhibits it in a more powerful manner is β-tetrahydro-naphthylamine—



It appears that its physiological effect is not only similar but due to the same process in the body, namely, increased heat production by central stimulation. It does not occur in animals under the influence of chloral.

5. Mydriatic Action. This action is due to a stimulating effect on the motor nerves to the dilator fibres of the iris, and thus cannot be abolished by muscarine. Its exact relation to the chemical structure of the molecule of cocaine is not known, but it appears to be derived from the ecgonine ring, which, though not generally mydriatic, causes some dilatation of the pupil in cats. The benzoyl group is essential for the appearance of this action. It is probably dependent on the structural arrangement, which is associated with the rise of temperature, as β-tetrahydro-naphthylamine is also mydriatic.

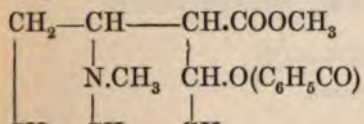
6. The effect on muscular action which has been attributed, apparently with accuracy, to cocaine, has not been shown to depend on any special chemical groups contained in the molecule. It may, perhaps, be attributed partly to the true stimulant action of cocaine on the central nervous system, which is accompanied by a decrease in nitrogenous elimination. A diminution in the oxidizing processes in the body is said to follow on the administration of the drug.

7. By far the most important physiological attribute of cocaine from a practical point of view is its power of producing local analgesia and anaesthesia. Not only pain but all sensations are affected; for instance, taste is abolished when cocaine is applied to the mucous membrane of the mouth, and heat and cold cannot be felt.

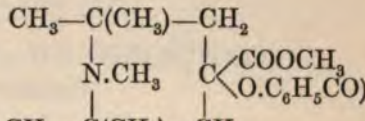
The local anaesthetic action of cocaine depends partly on the structure of the ecgonine nucleus, and partly on the presence and relative positions of the two substituting groups.

The ecgonine nucleus is possibly the least important factor in the production of anaesthesia, as it has been found that many other

substances, provided they possess similar substituents, can produce this effect. Various theories have been put forward to explain the part played by the ecgonine ring, several of which have subsequently been disproved. The most striking feature of ecgonine is its arrangement in a double ring, and this suggested itself as a causal factor in the physiological action of cocaine. However, a substance, *n*-methyl-benzoyl-oxy-tetramethyl-piperidin-carboxyl-methyl-ester, is a local anaesthetic, though containing but a single ring—

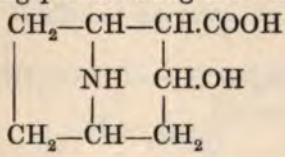


Cocaine.



n-Methyl-benzoyl, &c.

In fact, it has been found that a large number of substances, such as phenol, *para*-chlorphenol, picric acid, salicyl-methyl-ester, phenacetin, &c., have anaesthetic or analgesic properties. The simplest body producing these effects is the methyl ester of benzoic acid, $C_5H_4COOCH_3$. The $(N.CH_3)$ group may be replaced by (NH), the resulting product being nor-*l*-ecgonine—

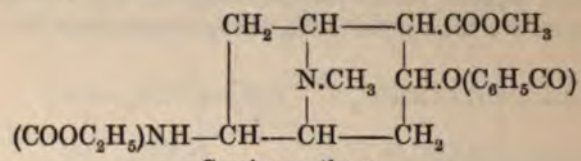


This, when benzoyl and methyl groups are introduced, as in ordinary cocaine, produces nor-cocaine, a powerful anaesthetic, but too toxic for practical purposes—the toxicity probably being due to the presence of the imide group (NH)".

That the ecgonine ring has its influence on the anaesthetic properties of cocaine seems to be shown by the fact that certain alterations, not affecting the substituting groups, may be accompanied by alterations in the anaesthetic potency of cocaine. Thus its conversion into a quaternary base by the addition of methyl-iodide destroys the distinctive cocaine action, and substitutes a curare-like one in its place.

ortho-Chlor-cocaine and *meta*-nitro-cocaine have only slight anaesthetic properties; *meta*-oxy-cocaine has no anaesthetic action, but is slightly toxic, and in large doses produces degeneration of the liver cells. The *meta*-amido compound produces neither anaes-

thesia nor destruction of liver cells. The latter property can, however, be restored by introducing benzoyl or acetyl into the amido group, and a powerfully anaesthetic body is produced by this means. By the action of chlorformic ester on the amido derivative, cocaine-urethane is produced, a strong anaesthetic, acting on the liver characteristically, and giving rise to toxic symptoms—



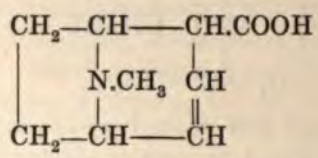
Cocaine urethane.

The ($CH_3.COO$) group is essential to the action of cocaine, as activating the inhibitory carboxyl group. It may be replaced by other acyls.

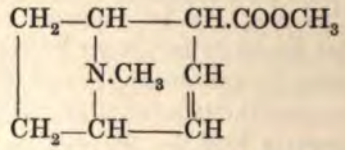
Thus coca-ethyline, containing the (C_2H_5COO) group, coca-propyline (C_3H_7COO), coca-*iso*-butyrine, &c., have been prepared, but have no advantages over cocaine in practice.

Benzoyl-ecgonine, benzoyl-nor-ecgonine, and ecgonine itself, have no anaesthetic action.

By the abstraction of water an anhydride of ecgonine can be formed,



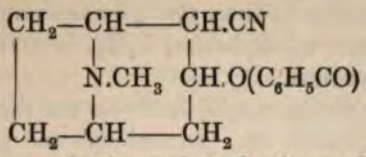
which, like ecgonine, has no anaesthetic action. Its ester is also inactive—



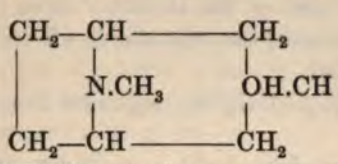
In the first case the inactivity may be explained by the presence of the carboxyl group. In the second case this explanation cannot hold good, and recourse must be had to the *essential* change in the ecgonine ring, and possibly to the presence of the double bond.

The ($CH_3.COO$) group has also been thought to exercise a specific strengthening effect on the physiological action. This view may

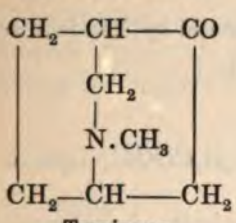
be supported by the fact that *laevo*-rotatory benzoyl-ecgonine-nitrile, though anaesthetic, is comparatively weak in its action—



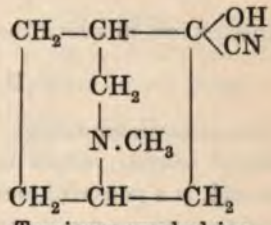
As against this are the facts that the benzoyl ester of pseudo-tropine,



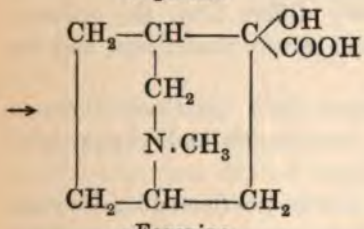
which contains no (CH_3COO) group, is a powerful anaesthetic (though tropine-benzoyl-ester is a weak one), while the methylated benzoyl ester of α-cocaine (an isomeric body obtained from tropinone) has no anaesthetic action.



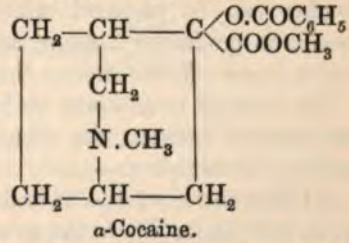
Tropinone.



Tropinone-cyanhydrine.



α-Ecgonine.



α-Cocaine.

It would be safer, therefore, to attribute the weakening of the physiological action of the nitrile of *laevo*-rotatory benzoyl-ecgonine to some actual antagonistic effect of the (CN)′ group, similar to that of the original carboxyl.

The importance of the benzoyl group is shown by the fact that in its absence no anaesthetic effect occurs, and moreover many substances containing it, such as benzoyl-tropine, the benzoyl derivatives of morphine, hydro-cotarnine, quinine, and cinchonine

are local anaesthetics. In the ecgonine derivatives it cannot act without simultaneous replacement of the carboxyl by a COOR group, and the presence of these two groups alone in such a simple substance as benzoic methyl-ester, $C_6H_5COOCH_3$, is sufficient to produce local anaesthesia.

In accordance with the nomenclature of the theory of dye-stuffs, it is called by Erhlich the 'anaesthiophore' group, while the ($N.CH_3$) group he calls 'auxotox' (see p. 22). The former cannot be replaced by any acid of the aliphatic series; and if replaced by another aromatic acid, the anaesthetic effects are either abolished or much diminished.

Phenylacetyl ($C_6H_5CH_2CO$) ecgonine has a slight anaesthetic action.

Again, atropine has slight anaesthetic properties. This is a compound of tropeine with tropic acid—

$$C_6H_5 . CH\begin{matrix}COOH\\CH_2OH\end{matrix}$$

Homatropine, in which tropic acid is replaced by mandelic acid,

$$C_6H_5 . CH\begin{matrix}COOH\\OH\end{matrix}$$

has more anaesthetic action.

Benzoyl tropine, where benzoic acid, C_6H_5COOH, replaces the tropic acid, is a powerful local anaesthetic.

Cocaine exists naturally as a *laevo*-rotatory body. A *dextro*-rotatory cocaine can be prepared which only differs from the ordinary cocaine in producing a more rapid and intense anaesthesia, and one which passes off in a shorter time.

The general conclusions to be drawn from the observations on the relation between the chemical constitution and physiological action of cocaine are:—

(1) The action on the central nervous system (including the vaso-motor effect) are due to the pyrrolidine ring, from which cocaine is originally derived.

(2) The peculiar action on the liver is a special attribute of ecgonine, and is partly dependent on the presence of tertiary nitrogen.

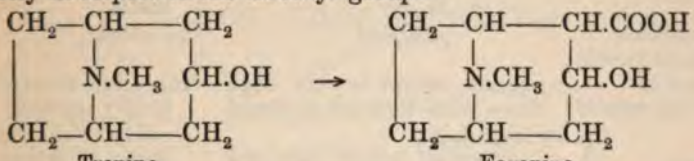
(3) The elevation of temperature and the peculiar effect on muscular energy cannot be traced to any special chemical factors.

(4) The mydriatic effect also is not yet accounted for in the chemical structure.

(5) The anaesthetic effect is largely dependent on the presence of the alkyl and benzoyl radicals, but is also due to the ecgonine ring, as this cannot be materially altered without destroying or diminishing this action. Of all these factors the presence of the benzoyl group appears to be the most important, as numerous other compounds containing this radical exhibit a similar pharmacological effect.

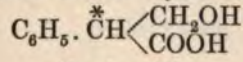
ATROPINE.

The chemical similarity between atropine and cocaine is accompanied by a physiological similarity which is no less remarkable. Both are esters combined with bases which differ from one another merely in respect of one carboxyl group—



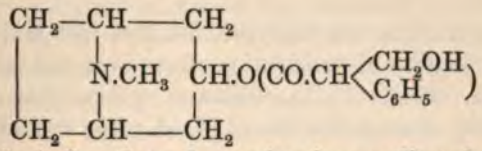
Tropine. Ecgonine.

Atropine is the ester of tropine and tropic acid, the latter body containing a benzyl nucleus and an asymmetric carbon atom—



Tropic acid.

Thus **atropine** is—



The physiological action of atropine is complicated; its effects on the organism depend largely on dosage, and divergent views are still held on the details of its mode of action. Atropine acts firstly on the central nervous system, producing (in large toxic doses) delirium, followed by profound depression. In small medicinal doses its action on the cerebrum is generally not noticeable. Toxic doses also raise the temperature, sometimes to a very considerable extent. Its peripheral action paralyses the terminations of the nerves to secretory glands and unstriped muscle (including the sphincter iridis in mammals); it has some action on sensory nerve endings, but on the nerves supplying striped muscle it has practically no action. It also paralyses the vagus terminations to

the heart. The comparison between atropine and cocaine may thus be set forth in tabular form :—

	Atropine.	Cocaine.
Cerebral and medullary centres	(large doses) deliriant (smaller doses) no sedative effect (final action) profound depression	deliriant sedative profound depression
Cardiac vagus terminations	depressant	depressant
Temperature	raised	raised
Bloodvessels	contracted (central) (rise of blood pressure)	contracted (central) (rise of blood pressure)
Eye	powerful mydriatic	less powerful mydriatic
Sensory nerves	slight local anaesthetic	powerful local anaesthetic
Nerves to unstriped muscle	paralysed	no action
Nerves to striped muscle	no action, except in very large doses, when they are paralysed	no action, except when locally applied
Muscle	by large doses, unstriped muscle paralysed by small, ,, ,, stimulated striped muscle, unaffected	possibly increases power of action in striped muscle
Nerves to secreting glands	paralysed	no action, unless applied locally to glands, when secretion is paralysed
Liver	no special action	specific degeneration (mice)

When these actions are analysed, the first fact which is brought out is that the general toxic action of atropine and cocaine is somewhat similar. The excitation, followed by depression of the cerebral and medullary centres, the rise of blood pressure and temperature, and the inhibitory action on the vagus terminations seem common characteristics of the two drugs. The mydriatic and local anaesthetic actions differ mainly in degree.

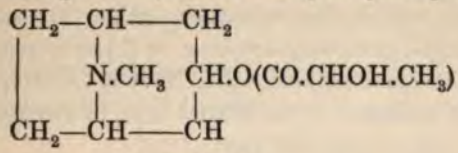
The action of atropine on unstriped muscle is to a certain extent analogous to the action of cocaine on striped muscle. Very small doses of atropine stimulate involuntary muscle fibres and increase their conducting power: cocaine taken internally has probably a stimulating effect on voluntary muscle, and here the dose which actually reaches the muscle must be very small.

The main differences are, then, the characteristic action of atropine on the nerves to unstriped muscle and secreting glands (though cocaine is said to act on these glands when locally applied), and the

no less characteristic action of the ecgonine derivative on the liver cells.

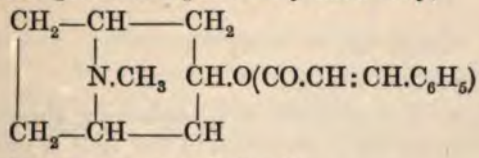
We can now proceed to consider the physiological action of atropine in detail.

(1) **Central actions.** Generally the action of atropine on the higher cerebral centres and also on those in the medulla is primarily one of stimulation, followed eventually by depression. This action may be attributed in part to the tropine nucleus, as, though but slightly toxic, such action as it has is entirely central. Tropine combined with aliphatic acids gives rise to a series of tropeines with central stimulating action; one of them, lactyl-tropeine,



has been used as a cardiac stimulant.

Cinnamic acid produces a powerfully toxic body,



which also only possesses a central action.

This primary stimulating action may therefore be considered as derived partly from the tropine ring, but it is much intensified by the addition of certain side-chains. The rise of blood pressure is possibly a pyrrolidine effect, as in cocaine, while the rise of temperature, observed in both atropine and cocaine, is as yet incapable of any satisfactory correlation with their chemical structures. It is remarkable, however, that it is frequently associated with a mydriatic effect of peripheral origin.

(2) It is to the peripheral action of atropine that the greatest attention has been paid by investigators, owing to its therapeutic importance. Generally, it may be described as involving depression of the nerve endings to involuntary muscle, secreting glands, and the sensorium.

(i) **Paralysis of nerve endings to involuntary muscle.** It is to this power that the important practical effect of atropine is due —the power of dilating the pupils and paralysing accommodation. The tropine nucleus must be considered as playing some small part

in this, as in toxic doses it causes mydriasis in cats. But it is only when tropine is combined with certain aromatic acids that the full effect is obtained. These aromatic acids all resemble one another in containing alcoholic hydroxyl. Thus the combinations with

tropic acid (forming **atropine**), $C_6H_5CH\langle^{CH_2OH}_{COOH}$

mandelic acid (forming **homatropine**), $C_6H_5CH\langle^{OH}_{COOH}$

and atrolactinic acid $C_6H_5C\langle^{OH}_{CH_3}{}_{COOH}$

are all mydriatic, whilst those containing either (1) no aromatic acid, like lactyl-, acetyl-, or succinyl-tropeine, or (2) an aromatic acid without hydroxyl, like cinnamic acid, $C_6H_5CH:CH.COOH$, or (3) an aromatic acid with hydroxyl of the phenol type, like salicyl-tropeine,

$$\begin{array}{l} CH_2—CH——CH_2 \\ \quad\quad\ |\quad\quad\ | \\ \quad\quad N.CH_3\ \ CH.O(CO.C_6H_4.OH) \\ \quad\quad\ |\quad\quad\ | \\ CH_2—CH——CH_2 \end{array}$$

are without mydriatic action.

The influence of an aromatic acid containing alcoholic hydroxyl in calling forth mydriatic properties in the base is not confined to the derivatives of tropine, but also occurs in such allied substances as *n*-methyl-triacetone-alkamine[1] and *n*-methyl-vinyl-diacetone-alkamine, of which the mandelic acid esters are mydriatic, but only in one stereo-isomeric form.

The principle thus illustrated, which is known as 'Ladenburg's generalization', may thus be expressed:—'Those tropeines only are possessed of mydriatic action which are combined with an acid side-chain possessing a benzene ring and an aliphatic hydroxyl.'

Marshall, Jowett and Hann, and Jowett and Pyman[2] have shown that this generalization is not absolute. Thus terebyl tropeine (in following formulae R = tropine radical),

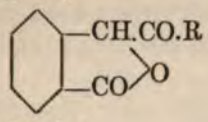
$$\begin{array}{l} (CH_3)_2:C—CH.CO.R \\ \quad\quad\ |\quad\ | \\ \quad\quad C\quad CH_2 \\ \quad\quad\ \diagdown\ \diagup \\ \quad\quad\ CO \end{array}$$

[1] The hydrochloride has been introduced into medicine as euphthalmine (see pp. 306, 316).

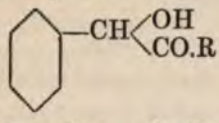
[2] *Trans. Chem. Soc.*, 1900, 1906 and 1907.

which contains neither a benzene ring nor aliphatic hydroxyl, is distinctly mydriatic, though its action is much weaker than that of atropine.

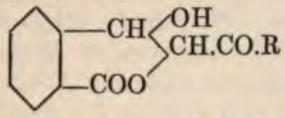
Phthalide-carboxyl-tropeine,



which is similar to homatropine,

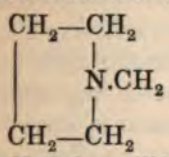


has also marked mydriatic action. On the other hand, the lactone of *o*-carboxyphenyl-glyceryl-tropeine,

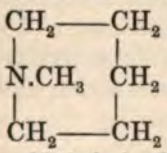


which contains a benzene group and alcoholic hydroxyl, is only feebly mydriatic; intravenous injections are moderately active, but not direct instillations into the conjunctiva.

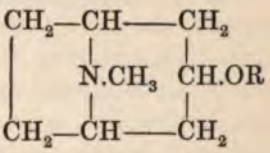
The relative position of the benzoyl and nitrogen groups appears to be of importance. Tropine, like ecgonine, is a combination or condensation of two rings, a pyrrolidine and piperidine. It is to the latter that the side-chains are attached:—



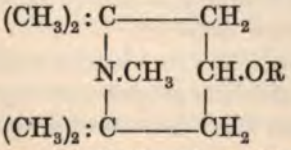
n-Methyl pyrollidine.



n-Methyl piperidine.

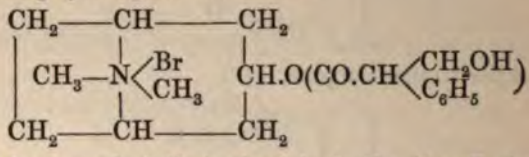


The radical R is in the *para* or γ position relatively to the nitrogen, and this is also the case with the alkamines having mydriatic action, thus:—



The mydriatic effect which is thus brought into action by the presence of certain side-chains is a property inherent in the parent

substance. Stereo-isomers are found to behave differently in this respect. Tropine exists, as has already been noted, in two such forms. The second, pseudo-tropine, forms with mandelic acid an isomer of homatropine which has no mydriatic action. Moreover, the addition of methyl bromide to the nitrogen group enfeebles the physiological action [1]:—



It must be remarked that, physiologically, the effect of atropine on the eye differs somewhat from that of cocaine. The effect of cocaine is to stimulate the dilator fibres supplied by the sympathetic, and only partially to paralyse the sphincter fibres from the oculo-motor nerve. There is no action on the ciliary muscle or on the light reflex. Atropine, on the other hand, certainly paralyses the sphincter nerve fibres and the circular muscle fibres of the iris themselves; it also abolishes the reaction for accommodation and light by paralysis of the nerve terminations in the ciliary muscle. Whether it also stimulates the sympathetic nerve fibres is a disputed point, and the experimental evidence has been variously interpreted. It seems more in consonance with the general physiological action of atropine to suppose that it has no exciting influence on the terminations of the dilator nerve.

The mydriatic action of atropine is clearly only part of its general action on the nerves to unstriped muscle, and on the unstriped muscle fibres themselves; and though direct evidence as to the chemical factors producing the well-known action of atropine on the intestine, bladder, &c., is not forthcoming, there is no reason to suppose that these factors are other than those which produce its effects on the eye. Its action on secreto-motor nerves is known to be distinct from the central action which raises the blood pressure. As, like the other peripheral effects of atropine, the secreto-inhibitory action is antagonized by pilocarpine, it may perhaps be assumed to rest on a similar constitutional basis.

Atropine is optically inactive; **hyoscyamine,** its isomer, exists in two forms, *dextro-* and *laevo*-rotatory. It is possible that the tropine nucleus in the isomers hyoscyamine and atropine is optically inactive,

[1] This substance, like homatropine, acts more rapidly and for a shorter time. This is due to more rapid absorption and excretion.

and that the isomerism of these substances depends only on the activity or inactivity of the tropic acid radical present; it has been suggested that in the living plant only *dextro*- and *laevo*-hyoscyamine occur, but that on drying these combine to give the inactive atropine. Considerable differences are observed in the physiological action of these optical isomers. In respect of the excitant action on the spinal cord :—

d-Hyoscyamine is strongest; then atropine; then *l*-hyoscyamine.

On the other hand, in respect of the action on the iris, secreting glands, and the vagus, the order is :—

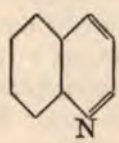
(1) *l*-Hyoscyamine; (2) atropine; (3) *d*-hyoscyamine.

The conclusion is that the action of atropine depends on its containing the two, *l*- and *d*-hyoscyamine, each of which exerts its specific physiological action.

(ii) **Paralysis of sensory nerve endings.** This is not so marked a property of atropine as of cocaine. Benzoyl tropine, which only differs from cocaine in the absence of the $COOCH_3$ group, is a local anaesthetic, though not so powerful as cocaine. Its isomer, benzoyl pseudo-tropine (tropo-cocaine), is a more powerful local anaesthetic than cocaine. Aliphatic esters of tropine have no anaesthetic properties. Thus in atropine, as in the substances which have been enumerated when dealing with cocaine, the benzoyl group seems to be of great importance in calling out the anaesthetic power of the base.

III. THE QUINOLINE GROUP.

The alkaloids belonging to this group form the chief active principles of cinchona and nux vomica. The parent substance, quinoline



has an action which somewhat resembles that of quinine, as it is an antiseptic and antipyretic. It cannot, however, be used therapeutically, as it provokes vomiting, and even in small doses is liable to produce collapse, respiratory disturbances, and oedema of the lungs.

Quinoline has a marked antiseptic action; it also affects the

metabolic cell processes so that the intake of oxygen is decreased, and the amount of energy produced is diminished; thus the heat production is lowered.

Compared with quinine, however, it is a feeble antipyretic, with little action on the malarial parasite; in pneumonia it completely failed to reduce the temperature (Brieger).

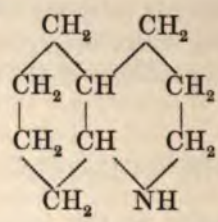
·6–1·0 gram produces paralysis of voluntary muscles and loss of reflexes in rabbits, and is eventually fatal. Quinoline is not excreted as such, but appears in the urine in the form of a body precipitable by bromine, stated by Donart to be carboxypyridine.

The action of hydrogen when added to the quinoline molecule is the same as was noted with pyridine.

Tetrahydro-*p*-oxy-quinoline kills rabbits in two hours in doses of ·6 gram; a similar dose of *p*-oxy-quinoline has hardly any effect.

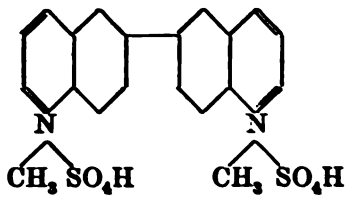
iso-Quinoline, quinoline, and pyridine present some remarkable analogies. The first two are not only similar in physiological action, but identically acting compounds may be derived from either, an important practical point owing to the expensiveness of the first-named body. Hydration has a similar intensifying effect on all three.

Decahydro-quinoline,

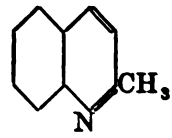


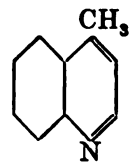
is a powerful blood poison, even in small doses. Generally, quinoline and pyridine act more powerfully on the central nervous system, and on the heart, whereas decahydro-quinoline and piperidine have a more rapidly destructive effect on the red blood cells. Hexahydro-quinoline, an intermediately placed body, more closely resembles the non-hydrated base. It has marked action on the heart and nervous system, and less on the blood.

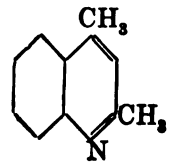
As a rule, the quinquevalent nitrogen derivatives of quinoline and *iso*-quinoline do not show a curare-like action, thus contrasting with the corresponding aniline derivatives, and the bodies obtained from the natural alkaloids. The methyl iodides of both quinoline and *iso*-quinoline, oxyethyl-quinoline-ammonium chloride and diquinoline-dimethyl-sulphate,

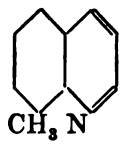
Quinotoxine 

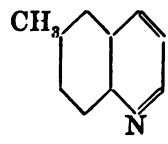
(a body containing two quinquevalent nitrogen atoms) are exceptions, and all act like curare.

Quinaldine (α-methyl-quinoline), 

lepidine (γ-methyl-quinoline), 

α-γ-dimethyl-quinoline, 

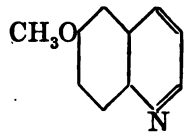
1-tolu-quinoline, 

and 3-tolu-quinoline 

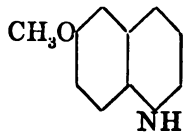
have been investigated by Stockman, who finds that the physiological activity as regards the nervous system varies inversely with the number of substituted methyl groups, but that the relative positions of the methyl and nitrogen are not of any importance.

The introduction of methoxyl in the *para* position in the benzene nucleus weakens the antipyretic action of quinoline.

p-Methoxy-quinoline, or *p*-quinanisol,



on reduction becomes **Thalline,**

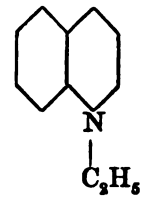


which has no specific action in malaria, is a powerful antipyretic and is also very actively destructive to the red blood cells. It produces, moreover, necrosis of the renal papillae, as do tetrahydro-quinoline, *ortho*-thalline, *ana*-thalline, acetyl-thalline, and its urea and thio-urea compounds.

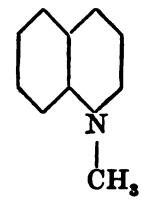
The introduction of an acid or alkyl radical into the NH group of tetrahydro-quinoline does not affect the physiological action.

The presence of OH groups in the benzene nucleus of the reduced quinoline compounds has the general effect of accelerating the antipyretic action and also of rendering it more transitory, possibly owing to more rapid absorption and elimination. Two substances illustrate these points:—

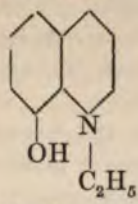
Kairolin A, or *n*-ethyl-tetrahydro-quinoline,



and **Kairolin B,** or *n*-methyl-tetrahydro-quinoline

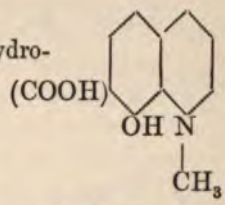


(in the form of sulphates) are not so rapid in action as **Kairine,** or *n*-ethyl-1-hydroxy-tetrahydro-quinoline—

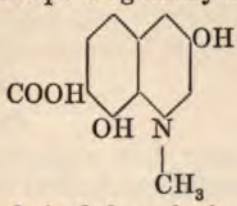


These substances are practically useless, owing to their destructive action on red blood cells; they do not, however, act on the kidneys. The introduction of a carboxyl group produces a powerfully antiseptic substance, the sodium salt of which has an action on the heart and arterioles, raising the blood pressure and slowing the pulse—

n-methyl-hydroxy-2-carboxy-tetrahydro-quinoline



It is excreted as the corresponding di-oxy derivative—

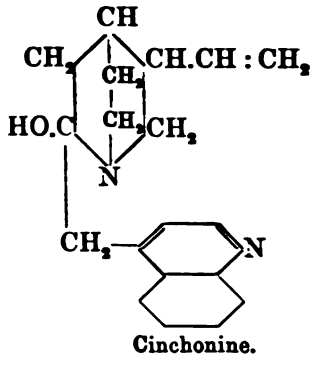


Of all the alkaloids derived from bark, quinine and cinchonine are the only two of which a detailed account need be given. Physiologically, quinine is characterized by its action as a protoplasmic poison; possibly it checks oxidation processes in the cell (Binz), and to this may be due its value in protozoic diseases. It also poisons the leucocytes, and in large doses acts as a gastro-intestinal irritant. It has a direct action on the walls of the blood-vessels and heart; in small doses it quickens the pulse and slightly raises the blood pressure, but in large doses it produces a gradual fall and finally cardiac failure. Some vaso dilatation probably occurs towards the end. The effect of quinine on the uterus is analogous to its action on other muscular structures; that is, it has a direct action, but here individual variations in reactivity are great. It

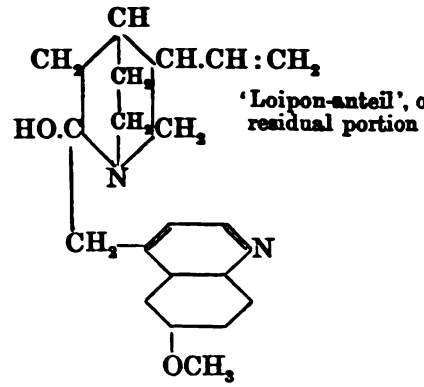
poisons the cells of the nervous system, and the effects of quinine on the special senses must probably be attributed to a direct action on the sensory epithelium. General metabolism is certainly depressed, as might be expected from a protoplasmic poison. There is also diminished heat production and probably increased heat loss.

Quinine, $C_{20}H_{24}N_2O_2$, and **Cinchonine**, $C_{19}H_{22}N_2O$, differ chemically in that a hydrogen atom in cinchonine is replaced in quinine by oxymethyl; physiologically, quinine is much the more active. Both consist of two parts, a quinoline ring, the existence of which has long been established, and a residual part, the constitution of which is still a matter of discussion.

Skraup gives the following formulae:—



Cinchonine.



Quinine.

Cinchonine is more toxic than cinchonidine, its *laevo*-rotatory isomer, and than the two oxycinchonines of Hesse and Langlois. The methyl group, however, which constitutes the chemical difference, does not in itself seem to produce the typical quinine effect; it may be replaced by ethyl, propyl, or amyl, with an intensification rather than a diminution of physiological action.

Cupreine, an alkaloid found in an allied species of plant, the remijia, has considerable resemblance to quinine and cinchonine,

Cupreine, $C_{19}H_{20}N_2.(OH)_2$,
Cinchonine, $C_{19}H_{21}N_2.OH$,
Quinine, $C_{19}H_{20}N_2.OH.OCH_3$,

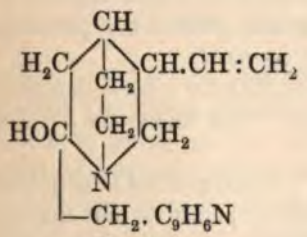
quinine being methyl-cupreine.[1] Cupreine is less active physiologically even than cinchonine, and only half as toxic as

[1] Schmiedeberg.

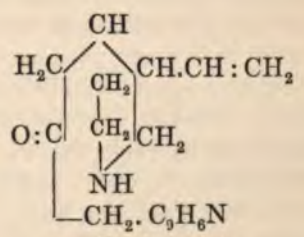
quinine, but its alkyl substitution products are active, as are the homologous quinine bodies. It thus appears that the alkyl groups merely act as a protective to the hydroxyl, and the fact that the higher alkyls are more active than methyl may be explained by the relative difficulty with which the latter is oxidized.

It is thought that in the organism part of the cinchonine is oxidized to cupreine, the introduction of OH in the *para* position being a usual form of oxidation in the body, and that thus the typical quinine action is produced. The largeness of the dose of cinchonine necessary to produce a marked effect is thought to be due to the small amount of cupreine formed. The artificial removal of CH_3 from quinine does not result in cupreine, but in an isomeric body, apoquinine, though conversely it is possible to produce quinine from cupreine. The small amount in which the latter substance occurs in nature prevents this being a practically valuable procedure.

It is not, however, now thought that the specific quinine action is due to the quinoline portion, but to the residual portion of the molecule, the so-called 'Loipon-Anteil'; and in this portion certain groups are considered to be the principal factors. It is possible, for instance, to convert the C.OH group in cinchonine into CO, this results in the formation of an NH group and the rupture of the ring complex. The product is known as cinchotoxine, and is entirely without the physiological action of quinine; it is very much more toxic, and somewhat resembles digitoxin—



Cinchonine.



Cinchotoxine.

But it cannot be decided whether the characteristic effects of quinine are lost owing to the breaking of the ring or the appearance of the ketone group in place of the alcoholic hydroxyl.

The vinyl group is not apparently of importance in determining the general toxicity, but it is remarkable that quinine is the only antipyretic drug containing a side-chain with a double bond.

S. Fränkel has synthesized a body (acetylamino-safrol) resembling phenacetin, but containing an allyl group, but though it appeared to reduce the temperature in experimental animals, it had no action resembling that of quinine in malaria.

It must be remembered that the so-called antipyretic action of quinine is to a large extent due to its toxic action on lower organisms, such as the plasmodium malariae. It is this action really which places it at the head of the list of antipyretics. It has, however, been shown experimentally to possess a slight power of reducing temperature, apart from any paraciticidal action. This is most probably a result of diminishing heat production due to a general inhibition of protein metabolism; in other words, by a toxic action on living protoplasm.

It is, however, probable that the double bond is associated here as elsewhere with considerable physiological activity. The body known as quitenine, in which vinyl is replaced by carboxyl,

$$\underset{\text{Quinine.}}{C_{18}H_{21}N_2O_2—CH:CH_2} \xrightarrow{\text{Oxidation}} \underset{\text{Quitenine.}}{C_{18}H_{21}N_2O_2—COOH}$$

has very little action as a protoplasmic poison, but whether this is due to the presence of carboxyl, the absence of vinyl, or both, cannot be decided.[1]

It is clear, however, that the residual portion of the quinine molecule is the one on which its physiological action depends, and that the quinoline portion merely acts as a link which enables it to exert its specific action; in the quinoline portion the presence of oxymethyl in the *para* position is also essential.

Quinidine is a *dextro*-rotatory quinine, with a similar action physiologically. It is also, however, narcotic. The numerous isomers of cinchonine produce convulsions.

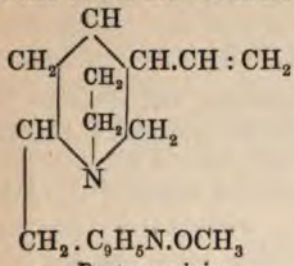
Hydroquinine, in which hydrogen is introduced into the quinoline ring, is a very poisonous body, producing paralysis and inhibiting respiration in quite small doses. Half a gram subcutaneously has been fatal to an animal.

Desoxy-quinine, a substance which differs from quinine in containing no hydroxyl in the residual portion, gives all the reactions

[1] Hunt, however, has shown that quinine derivatives in which the vinyl group has been altered to $.CH_2.CH_3$, $.CHOH.CH_3$, $.CHCl.CH_3$, have the same toxic action as the parent substance on infusoria (Archiv. Internat. de Pharmacodyn. Bd. 12. 1904).

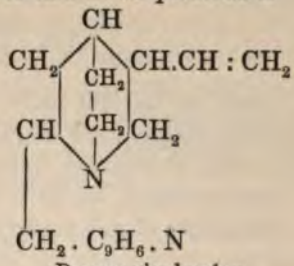
of quinine. A corresponding substance can be formed from cinchonine.

These bodies are ten times more toxic than their precursors.



$CH_2 . C_9H_5N.OCH_3$

Desoxy-quinine.



$CH_2 . C_9H_6 . N$

Desoxy-cinchonine.

SUBSTITUTES INTENDED TO REPLACE QUININE.

Apart from the occurrence of the toxic symptoms known as 'cinchonism', which the administration of quinine may produce, this drug has two special drawbacks in practice, its intensely bitter taste and its relatively insoluble character. Hence a number of salts of quinine and other compounds have been introduced, on the one hand with a view of abolishing the taste, and on the other of increasing the solubility of the drug. As a matter of fact these two aims are not compatible with one another. The only quinine compounds which are tasteless are the insoluble ones. In the soluble salts of these compounds the characteristic bitter taste is restored. For convenience, therefore, quinine substitutes will be divided into two classes, the insoluble ones intended for oral administration, and the soluble ones suitable for hypodermic or intravenous injection.

I. Insoluble in Water.

Among the ordinary salts, the tannate, an amorphous powder obtained by acting on the sulphate with a tannic acid solution, is practically tasteless. It is, however, uncertain in its action, and is first broken down in the small intestine. Esters formed from the hydroxyl group in the residual portion have also been produced. **Euquinine** is the propionic acid ester of quinine, is practically tasteless, and is said not to irritate the stomach. A carbonic acid ester of diquinine is known as **Aristoquin.** This body is soluble in dilute acids, so that it dissolves in the stomach; it is not reprecipitated in the intestine.

$C_2H_5COO.OC_{20}H_{23}N_2O$

Euquinine.

$CO\langle^{O.C_{20}H_{23}N_2O}_{O.C_{20}H_{23}N_2O}$

Aristoquin.

Aristoquin is not so rapidly excreted as the hydrochloride of quinine, and its toxicity for man is stated to be lower.

Saloquinine is the salicylic acid ester—

$$C_6H_4\begin{matrix}OH\\ \diagdown\\ COOC_{20}H_{23}N_2O\end{matrix}$$

It is said to be less active therapeutically, and to show unpleasant by-effects more frequently. The dosage must, of course, be double that of ordinary quinine. A salicylate of saloquinine has also been produced, which is insoluble, and is intended to combine the advantages of salicylates and quinine without their bitter taste. These two compounds are soluble in dilute acids, and are consequently decomposed in the stomach.

An *iso*-valeryl ester of quinine has also been synthesized, but is not on the market. It is similar to the salicyl compound.

Quinaphthol is β-naphthol-α-monosulphate of quinine—

$$(C_{10}H_6 . OH.SO_3H) . C_{20}H_{24}N_2O_2$$

and is a yellow powder, containing about 42 per cent. quinine, very slightly soluble in hot water and alcohol. It is decomposed in the intestine, and is primarily intended as an intestinal antiseptic.

Quinaphenin is quinine-phenetidin-carboxylic acid—

$$CO\begin{matrix}NHC_6H_4 . OC_2H_5\\ \diagdown\\ OC_{20}H_{23}N_2O\end{matrix}$$

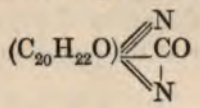
It is a white, very insoluble powder. Therapeutically it has no advantage, beyond that of tastelessness, over a mixture of the two bodies.

II. Soluble in Water.

Besides the ordinary salts of quinine, some of which are sufficiently soluble for hypodermic injection, two bodies have been introduced for this purpose, namely, **Quinopyrine** and **Quinine Hydrochloro-Carbamide.** The first of these is a compound of quinine hydrochloride, and antipyrine, and is a white powder easily soluble in water. It is unsuitable for internal administration, owing to its toxicity. The second is a compound of urea with quinine and hydrochloric acid, soluble in one part of water. Its disadvantage is that it contains very little quinine.

STRYCHNINE AND BRUCINE.

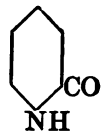
Our knowledge of the chemical structure of these two bodies is very imperfect. But little is known as to the nature of the carbon rings of which they are constructed, or as to the parts played by the oxygen and nitrogen. It appears probable that one nitrogen is situated in a reduced quinoline or indol ring, and that its basic character is modified by the presence of a carboxyl group. The formula for strychnine will be represented thus :—



The physiological action of **strychnine** is mainly on the cells of the spinal cord, whereby the resistance to the translation of slight sensory stimuli into reflected muscular action is removed. The evidence points to some structure between the anterior motor cells and the terminations of the sensory nerve fibres in the cord. Schäfer has described intermediate cells in the posterior horns which link the pyramidal tract with the lower motor neurons, and which are intimately connected with the sensory nerve endings in the posterior horns. Its action on the medulla may be said roughly to correspond to that on the cord, while, with regard to the cerebrum, the special senses appear to be rendered more acute, though there is no evidence to show how this takes place. Light and tactile impressions, the most easily tested, have been shown to be improved by small doses. The remaining actions of strychnine, though important therapeutically, are not of much theoretical interest, as they depend either upon the central action (e. g. vagus and vaso-constrictor effects), or on the convulsions (increased formation of carbon dioxide, and increased heat production). Of more interest, from the present point of view, is the action of strychnine on lower forms of life. The higher animals, owing to the preponderating effect of strychnine on the nervous system, show none of its action as a protoplasmic poison. But on protozoa its action is very similar to that of quinine, to which it is chemically related, and it is possible that its effects on higher invertebrates (e. g. Ascaris) are mainly due to its toxic action on protoplasm.[1]

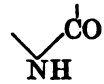
[1] Shrieder explains the resistance of some ascarides to strychnine as due to their closing their mouths when placed in a solution of the drug, which can thus act only through the skin.

Piperidon,



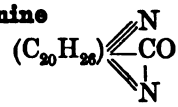
which is α-keto-piperidine, is stated by some authorities to have the same action on the spinal cord as strychnine. Its activity depends, as previously stated (see p. 246), on the closure of the ring; at any rate, δ-amino-valerianic acid, in which carboxyl is of course present, has no action.

The question whether the action of strychnine on the spinal cord depends upon the presence of the piperidon group



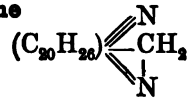
is complicated by the presence of the second oxygen atom in the strychnine molecule. Briefly, it may be said that the characteristic action depends on the presence of *both* oxygen atoms; removal of either lessens the activity, removal of both destroys it.

Thus **Desoxystrychnine**



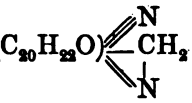
is more bitter than strychnine but less toxic.

Dihydrostrychnoline



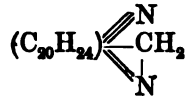
has no action on the cord.

Strychnidine



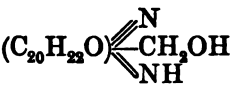
is bitter, and physiologically stands between strychnine and desoxystrychnine.

Strychnoline



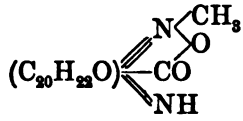
is inactive.

Electrolytic reduction of strychnine gives rise to two bodies (Tafel),

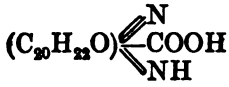
Tetrahydrostrychnine 

and strychnidine, of which the first is more powerful; both produce strychnine-like effect.

Methyl strychnine, a secondary base,

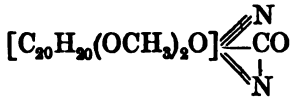


and *iso*-strychnic acid



act in exactly the same way as strychnine. The latter is fatal to frogs in doses of ·0005 gram: the former has no bitter taste; some authorities state that its action is similar to curare.

The alkaloid **Brucine**, which is dimethoxy-strychnine,



has a similar action to that of strychnine. It is, however, less powerful and its taste is less bitter.

CHAPTER XIV

The alkaloids considered. iso-quinoline group — Hydrastine, Berberine. Morphine ?-Phenanthrene group — Morphine, Narcotine and Opium Alkaloids. Berbamine.

IV. iso-QUINOLINE GROUP.

In this group are contained a number of alkaloids, the therapeutic effects of which differ considerably, in degree if not in kind. Some of them are derived from Opium,

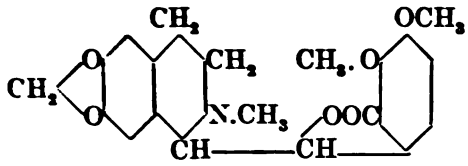
viz. Papaverine,
Narcotine,
Narceine;

others from Hydrastis Canadensis,

viz. Hydrastine,
Berberine.

The latter plant has been extensively used in order to arrest hæmorrhage, owing to its action as a vaso-constrictor, and it has also been employed in place of ergot to stimulate uterine contractions. It has thus very little in common with opium from the therapeutic point of view, and it is a curious fact that its alkaloidal principles should be so closely related chemically to some of those found in the last-named plant.

Hydrastine, $C_{21}H_{21}NO_6$, has the formula—



and differs from narcotine in possessing one methoxyl group less. Its physiological action is still a matter of some doubt, especially as regards its direct action on the muscular walls of the smaller blood-vessels and the uterus. In toxic doses it has an action resembling

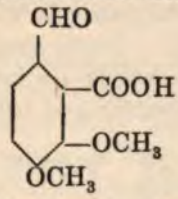
that of strychnine, but it is also a direct muscle poison and a gastro-intestinal irritant. In moderate doses, it stimulates and then paralyses the centres in the medulla and cord, and, after possibly a short stage of excitation, depresses both voluntary and involuntary muscle. Many authors assert that it has a direct ecbolic action. In medicine its main value lies in its action on the medullary centres, whereby the vagus, vaso-constrictor, and respiratory centres are stimulated, and the blood pressure rises. Its action on involuntary muscle, however, causes cardiac weakness, and the rise is not maintained for long.

Theoretically, its strychnine-like action is interesting, the latter alkaloid belonging to a group which is chemically so closely related (quinoline).

When hydrastine is decomposed, water is taken up, and two bodies, hydrastinine and opianic acid, are produced.

$$\underset{\text{Hydrastine.}}{C_{21}H_{21}NO_6} + H_2O = \underset{\text{Opianic acid.}}{C_{10}H_{10}O_5} + \underset{\text{Hydrastinine.}}{C_{11}H_{13}NO_3}$$

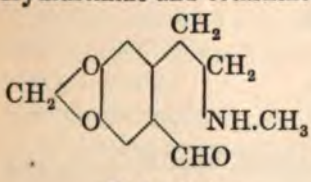
Opianic acid has the constitutional formula



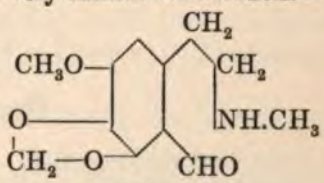
Similarly, narcotine yields opianic acid and cotarnine.

$$\underset{\text{Narcotine.}}{C_{22}H_{27}NO_7} + H_2O = C_{10}H_{10}O_5 + \underset{\text{Cotarnine.}}{C_{12}H_{15}NO_4}$$

Hydrastinine and cotarnine have very similar constitutions—



Hydrastinine.



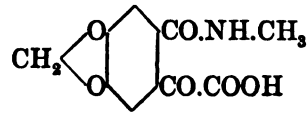
Cotarnine.

The position of dioxymethylene- and methoxy-groups are not known with certainty.

The aldehyde group CHO, in the formula for hydrastinine, best explains its physiological characters, most alkaloidal vaso-constrictors having this group (cf. yohimbine, which, however, has but a slight effect on the arterioles).

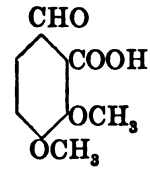
The action of **hydrastinine** differs markedly from that of its parent substance. It has no convulsant action, and it does not weaken the heart; on the other hand, it is a depressant of the cerebral cortical cells. Its action on the uterine muscle is not certain, nor is it yet decided whether it has any direct effect on the arterial walls. Its power of raising the blood pressure is more sustained owing to cardiac stimulation. It is also a mydriatic. Death occurs owing to respiratory failure. The action of hydrastine on the blood pressure may be regarded as part of its strychnine-like properties. Hydrastinine, on the other hand, has a more specialized power, and heightens the contractility of the cardiac muscle. The same effect, namely, a rise in blood pressure, is thus produced by a somewhat different means in the two bodies, and is moreover much more marked in hydrastinine. According to the aldehyde formula, it contains the group $-NH.CH_3$. It is thus a secondary amine, and contains a hydrogen atom replaceable by methyl. A pentavalent body of this kind, trimethyl-hydrastyl ammonium chloride, has been prepared. It has but little vaso-constrictor action; it produces a general paralysis, with an initial rise of blood pressure followed by a fall. Death occurs, as with curare, from paralysis of the respiratory muscles (peripheral).

An oxidation product, hydrastininic acid,



is physiologically inactive.

Opianic acid



has slight narcotic properties. It is almost inactive in the case of warm-blooded animals, but in the case of cold-blooded animals it produces narcosis, paralysis of central origin, and very slight muscular contractions. Its combination with the hydrastinine molecule seems to produce a diminution of physiological activity, as well as certain marked alterations in the latter which have already been noted.

Narcotine, Cotarnine, and Hydrocotarnine resemble other alkaloids of the morphine group; they may be considered here in

their relation to hydrastinine. Two of the salts of cotarnine have recently been introduced into medicine, the hydrochloride, known as **'Stypticin'**, and the phthalate, **'Styptol'**. These trade names indicate the use for which they are intended, but it is probable that that result is produced by these drugs in a somewhat different manner. Cotarnine hydrochloride, which retains slightly the narcotic properties of narcotine, has no vaso-constrictor action, nor does it increase the coagulability of the blood. Its effect as a styptic is thought to be due to its slowing the respiratory movements, whereby the blood stream is somewhat retarded and the formation of a clot favoured. The phthalic acid compound has also a distinct sedative effect, followed, if large doses are given, by convulsions, paralysis, and death. It has no action on the heart, but death occurs from respiratory failure. It is said to induce uterine contractions. It appears to have some direct action in checking capillary bleeding, for it is not a vaso-constrictor. This action is, at any rate, in part due to the phthalic acid,

$$C_6H_4\begin{matrix}COOH\\COOH\end{matrix}\ 1:2$$

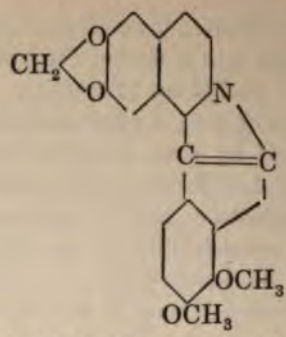
as neutral phthalate of ammonium acts similarly but not so powerfully.

Narcotine and hydrastine, with their various derivatives and compounds, act on the whole in very similar manner, and the secondary products correspond fairly closely with one another. The main points of difference are that all narcotine derivatives tend to reproduce the narcotine action of the original substance, while the products formed from hydrastine act most markedly on the arterioles and the blood pressure.

Methyl-narcotimide is a marked local anaesthetic; the amide is uncertain in its action on man, sometimes resembling morphine and sometimes codeine.

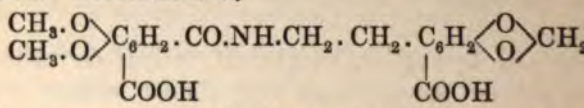
Methyl-hydrastamide is a vaso-dilator, and has been unsuccessfully tried as an emmenagogue.

Berberine, $C_{20}H_{17}NO_4$, the remaining alkaloid of hydrastis, has very little action in the amount in which it is present in the drug. 20 grams (300 grains) have failed to produce any symptoms in man. It is said to be completely decomposed in the body, thus differing from hydrastine, which is excreted unchanged in the urine. Its constitution is expressed, in all probability, by the formula—



Large doses lower the blood pressure, raise the body temperature, increase peristalsis, and finally produce general paralysis of central origin. As a constituent of hydrastis canadensis, it probably acts only as a 'bitter'.

Hydro-berberine, which contains four atoms more of hydrogen, is a vaso-constrictor, raising the blood pressure by its action on the centre in the medulla. It also produces convulsions of spinal origin before the final paralysis. The general change in physiological action produced by the addition of hydrogen is thus well illustrated. Berberilic acid,



like the corresponding oxidation product of hydrastine, is physiologically inactive.

V. MORPHOLINE(?)-PHENANTHRENE GROUP.

Alkaloids of Opium.

Opium is said to contain no less than twenty-one alkaloids, besides five non-basic substances, some of which are physiologically active. Besides these there are numerous alkaloidal bodies which have been artificially produced from the opium bases, and of these a few are of pharmacological importance.

Chemically, the opium alkaloids fall into two main groups, the *iso*-quinoline group and the phenanthrene group. Physiologically also, two main groups may be described, namely, those with the physiological attributes of morphine and those resembling thebaine. Unfortunately these two groups do not correspond in the very

least; both morphine and thebaine, for instance, belong chemically to the phenanthrene group.

Before considering the composition and properties of these bodies in detail, a few general observations may be made. Chemically, the question of the structure of morphine cannot be regarded as settled, as neither of the suggested formulae is in consonance with all the facts. Physiologically, much attention must be given to the details of any experiments on the action of these bases in the organism. The discordant results which have occasionally been obtained make it clear that much depends both on the size of the dose of any given alkaloid, and the species of animal employed in the experiment. For instance, originally C. Bernard described morphine as soporific and thebaine as tetanizing, and the other alkaloids have been classed as belonging to one or other of these groups. As a matter of fact, however, careful experiment with graduated doses has shown that all the opium alkaloids possess *both* actions, but that they are developed in very different proportions. Thus though Bernard's classification is very convenient and marks the main action of these bodies, it must be remembered that intermediary substances occur, and that in no substance is either the soporific or the tetanizing action entirely absent.

With regard to the various artificial products which have been constructed from morphine, it will be found that in general they only differ from that substance physiologically in a qualitative manner, so long as only the circumferential portions of the molecule are altered. If, however, the intimate structure is broken down, products will result differing entirely in their pharmacological properties (cf. apomorphine).

The principal alkaloids belonging to the phenanthrene group are:—

Morphine,
Codeine,
Thebaine.

Those of the *iso*-quinoline group are:—

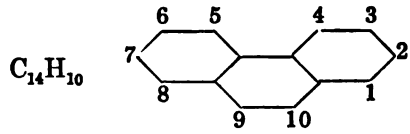
Papaverine,
Narcotine,
Narceine,
Laudanosine,
Laudanine,
Cotarnine,
Hydro-cotarnine.

Of these, narcotine, cotarnine and hydro-cotarnine have already been partially considered in connexion with the *iso*-quinoline group. They will, however, be briefly dealt with in this section in so far as their pharmacology connects them with the opium alkaloids.

Morphine, $C_{17}H_{19}NO_3$.

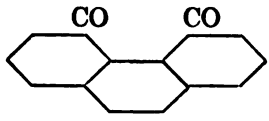
Knorr's formula for morphine is based on its apparent origin from two bodies, phenanthrene and morpholine, just as cocaine and atropine originate in a double-ring tropine.

Phenanthrene is represented by the formula



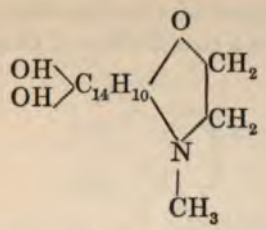
The numbers indicate the method of nomenclature of its derivatives.

For dogs this substance is inert, and after oxidation is eliminated as a compound of glycuronic acid. This reaction, however, appears not to be universal, as in some animals it has a narcotic effect. If, however, one or more hydroxyl groups are introduced, e.g. 2, 3, and 9-phenanthrol, substances are obtained producing severe tetanic convulsions in warm-blooded animals. Phenanthrene-9-carboxylic acid, 4-methoxy-phenanthrene-9-carboxylic acid, and phenanthrene-3-sulphonic acid have a similar action. The introduction of more oxymethyl or acetyl groups, however, has the effect of lessening both the toxicity and the tetanizing action. It does not appear that any phenanthrene derivatives as yet known have any narcotic effect, though one compound of phenanthrene-quinone,

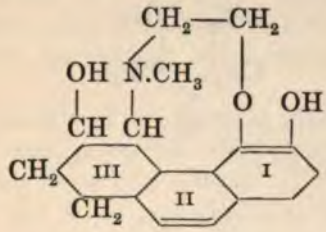


namely 2-brom-phenanthrene-1-sulphonic acid, is said to have a morphine-like action on the respiratory centre.

Morphine is supposed to be a derivative of tetrahydro-dioxy-phenanthrene, to which the morpholine complex is united. Knorr assigned to the alkaloid the structural formula—

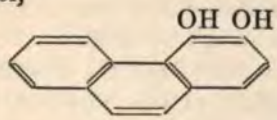


but more recent investigators have amplified their view of its constitution, and the following formula expresses in more detail the facts at present known (see also p. 302).

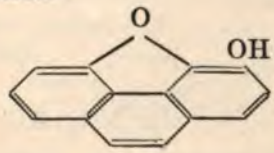


The three oxygen atoms have thus three different significations. That attached to the first benzene ring is in the form of phenolic hydroxyl; that connecting the phenanthrene with the morpholine ring is indifferent, corresponding to that in the ethers, and both of these may be traced in two decomposition products, the constitution of which is known.

The first is morphol,



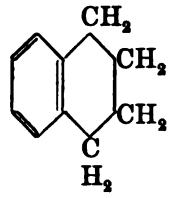
and the second morphenol—



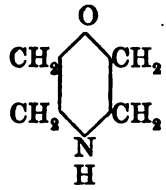
The oxygen connected with the third ring is united with H as simple alcoholic hydroxyl.

Naphthalan-morpholine, a substance isolated by Knorr, or one of its active alkyl substitution products, comes nearer to morphine

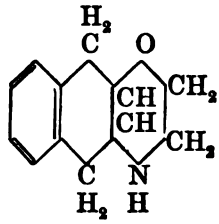
and codeine in its chemical relationships than any of the synthetic morpholine bases. It is a combination of tetrahydro-naphthalene,



and morpholine,

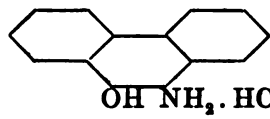


and has the formula—



S. Fränkel throws doubts on the resemblance between the physiological action of this substance and that of morphine on man, but Leubuscher[1] states that it is very close.

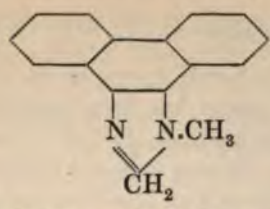
Vahlen, on the assumption that the phenanthrene nucleus was the more important portion of the morphine molecule, synthesized an amido-oxy-phenanthrene, to the hydrochloride of which he gave the name **Morphigenin**—



Many derivatives of this body were obtained which acted like morphine physiologically, but chemically they were not pure. One, however, called

[1] *Annalen*, 307, 172, 1899.

Epiosin



was said to have analgesic and slight narcotic action, and to produce convulsions, thus resembling codeine. It did not, however, slow the pulse, whereas it did raise the blood pressure, thus differing from morphine. There were also great quantitative differences, ·12 gm. corresponding to about ·3 gm. dionine. Pschorr, however, holds that all this work is at fault, and states that the original substance was not morphigenin but a nitrogen-free phenanthrene derivative.

It is to the presence of the phenolic hydroxyl group that morphine owes its acid properties. The hydrogen may be replaced by an alkyl group, or an acid radical. If this is done, a remarkable change in the physiological action takes place, and the characteristic narcotic effect is either much diminished or entirely lost. The narcotic effect of morphine on man is much more marked than on the lower animals, owing to the more complex development of the highest nervous centres, and its toxic effect is also, for similar reasons, far greater. The diminution of this action, and the increase in tetanizing power which accompanies any substitution of the hydrogen of the phenolic hydroxyl by another group, is due to a destruction of the 'anchoring' group for narcosis and not to the introduction of any new factor. That this is so may be seen from the facts that (1) any substitution product shows the same physiological effect, those compounded with inorganic acids are, however, rather more easily dissociated in the organism; (2) a dimorphine, in which two morphine molecules are united by an ethylene residue, e. g.

Ethylene-dimorphine,

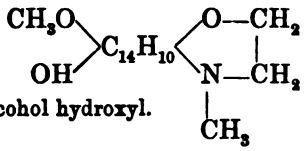
$$\left.\begin{matrix} C_{17}H_{18}NO_3 \\ C_{17}H_{18}NO_3 \end{matrix}\right\rangle C_2H_4$$

is without narcotic effect.

Of the numerous substances, both natural and artificial, more or less resembling morphine in action, it will only be necessary to mention a few which either illustrate a pharmaco-dynamic principle, or have been actually used in medicine.

Codeine, $C_{17}H_{18}NO_2 . OCH_3$.

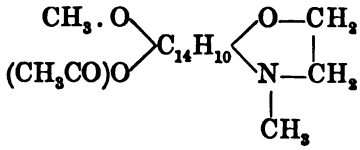
This is the methyl ether of morphine in which the hydrogen of the phenol-hydroxyl group has been replaced by methyl, and the constitutional formula for this alkaloid is consequently dependent on that of morphine. It was obtained in 1881 by Grimaux by the action of methyl-iodide and an alkali on morphine,



Owing to its small toxicity in man and its sedative action on the respiratory mucosa, it is largely employed in therapeutics. Experimentally, it stands midway between morphine and thebaine. It is much more toxic for animals than morphine. Metabolic processes seem to be less influenced, and constipation is not so marked.

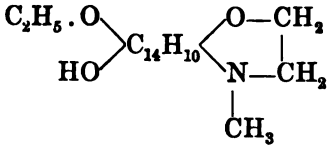
Codeine is incapable of forming an ether corresponding to the morphinether of morphine, in which linkage takes place through phenolic hydroxyl, as the distinctive methyl group would in that case be lost.

Acetyl codeine



has been prepared, but is practically useless, as it does not affect respiration and causes extreme reflex irritability (Dreser).

Dionine



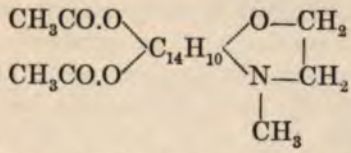
is the hydrochloride of ethyl morphine, and differs somewhat markedly from the numerous morphine substitution products which have been constructed and tested physiologically. In the first place it is very easily soluble in water, and is therefore suitable for hypodermic injection, and in the second place it is rather more powerful in its action than the corresponding methyl derivative (codeine). In this it illustrates a general practical rule, ethylic

compounds being usually more effective physiologically than those of methyl. Higher homologues and substitutions with aromatic radicals act less powerfully than codeine and dionine.

Dionine has also analgesic properties, and has been employed in ophthalmic practice. It is not a local anaesthetic, and occasionally sets up some irritation of the conjunctiva with considerable chemosis (Hinshelwood).

Heroine.

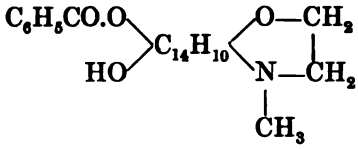
This is a diacetyl compound, both the alcoholic and phenolic hydroxyl groups being substituted. It is thus a diacetic ester of morphine—



Its action on the respiration is in some way selective, and is said to be more sedative than that of morphine. It is, at any rate, more powerful than codeine. The frequency of the respiration is diminished, and cough is checked. It has no marked anaesthetic action, but is generally soporific. Harnack, who objected to its use therapeutically, owing to its toxic properties, remarked that acetyl substitution products of hetero-cyclic compounds usually manifested high toxicity. This, however, is not exactly true, and the fact seems to be that the acetyl group renders a substance more toxic when it replaces hydroxyl hydrogen, and less toxic when it replaces amide hydrogen (S. Fränkel). Examples may be found in atropine, scopolamine, and homatropine, which are more toxic than tropine, and cocaine, which again is more toxic than ecgonine. The best example, however, may be found in aconitine, where the substitution of acetyl for the hydroxyl group converts an almost inert body into a powerful poison, while the introduction of two more acetyl groups has no effect except to slightly decrease the toxicity (Cash and Dunstan). Heroine is largely used owing to its specific action on the respiratory centre. The minimal fatal dose for rabbits is said to be a little larger than that of codeine (·1 gram per kilo. body-weight), but the minimal effective dose in practice is only one-tenth that of codeine. The hydrochloride is usually prescribed owing to its solubility. The mono-acetyl compound is not employed, it is more like morphine in its action, having less tendency to pro-

duce tetanic convulsions, greater hypnotic power, and less toxicity than heroine. It has, however, no special action on the respiratory organs.

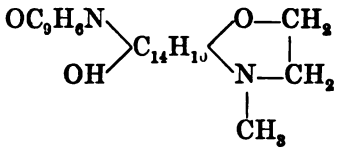
Benzoyl morphine—



The action of this compound is very similar to that of codeine, and thus illustrates the rule that the substitution products of morphine owe their physiological action to the fact that the anchoring group for the narcotic effect is partly covered, and that the group introduced for this purpose is of comparatively small importance. Practically, however, benzoyl morphine, which has been introduced into pharmacy under the name of **Peronine**, has the disadvantage of being less soluble than either heroine or dionine, and also of possessing a burning taste.

Less Important Artificial Derivatives.

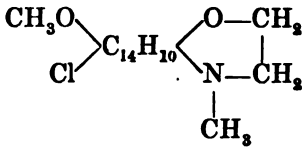
Morpho-chinoline ether



is interesting, though of no practical value. It has the main characteristics of codeine, causing spasm, especially of the respiratory muscles, and a rise of blood pressure. It acts through the centres in the medulla.

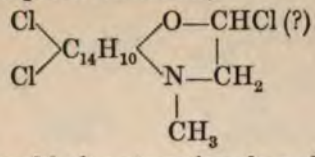
Chlorine and bromine have been substituted for various hydroxyl and hydrogen atoms, with the general result of destroying the narcotic effect.

The **chloride of codeine**



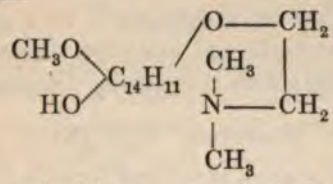
is a powerful muscle poison, in addition to possessing a general codeine-like action. This is supposed to be due to the halogen,

which is known as a muscle poison (as for example in $CHCl_3$), but it is curious that morphine trichloride,



which contains three chlorine atoms is only a slight muscle poison.

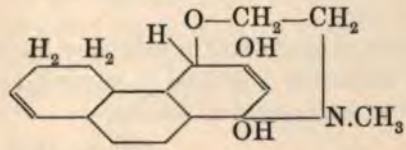
Metho-codeine—



The ring-structure in this compound is broken, with a consequent change in the physiological action. There are no narcotic and tetanizing actions, but only muscle poisoning and slight depression of the cord. There is some blood change also, so that the urine becomes deep green. It thus clearly resembles apomorphine, except that it produces no vomiting; it was formerly considered to be identical in composition with that body.

It has no action on the pupils, but depresses the respiratory centres like morphine; unlike that drug it increases the blood pressure, and frequency of the heart. Its stereo-isomer has a similar action.

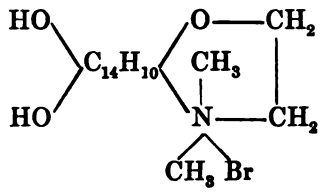
iso-**Morphine** is a substance obtained, together with small quantities of an isomeric derivative *β-iso*-morphine, by the action of water on brom-morphine. The following formula has been suggested:—

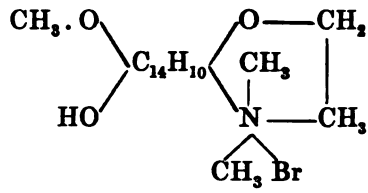


The corresponding *iso*-codeine has also been prepared, but neither of these derivatives has any narcotic action, even when given in gram doses. If the constitutional formula given above is correct, the failure in physiological action may be attributed to the change in position of the morpholine ring, which is there represented as attached to one benzene nucleus only.

Compounds of morphine and codeine, in which the nitrogen is

quinquevalent, have been investigated. They are the so-called brommethylates and have the formulae—

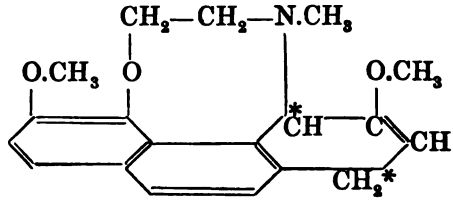




Physiologically, they are characterized by a great diminution of toxicity, due to their rapid and complete elimination in the urine. In cats the tetanizing action is especially diminished.

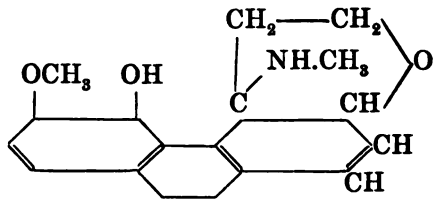
Thebaine, $C_{19}H_{21}NO_3$.

This substance, a possible structural formula for which is written below, is not only physiologically different from morphine, as it produces practically no narcosis and is an active tetanizing agent, but differs also chemically in being derived from a dihydrophenanthrene, instead of a tetrahydrophenanthrene, and in having both its hydroxyl hydrogens replaced by methyl groups.



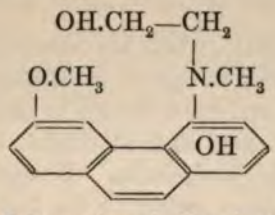
The fact that it does not produce a morphine effect is probably owing to the absence of an 'anchoring' OH group, as well as to differences in the number of hydrogen atoms combined with the phenanthrene ring.

By the action of dilute HCl, a substance known as thebenine can be produced, which has a general paralysing action. Its structure may possibly be represented as follows:—



* The position of these hydrogen atoms is not certain.

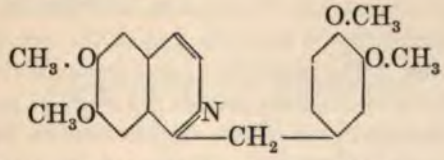
Concentrated hydrochloric or hydrobromic acids convert thebaine into an absolutely inert body, morphothebaine, $C_{18}H_{19}NO_3$, probably constituted—



The composition of these two bodies is, however, not definitely settled. It has been argued that morphothebaine, with its two free hydroxyls, should act like morphine, and hence another structure has been suggested, involving more profound changes in the nitrogen-bearing ring, and the presence of only one methoxyl group.

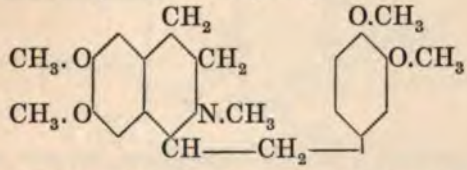
Opium Alkaloids containing an *iso*-Quinoline Ring.

Papaverine, in its physiological action, comes midway between morphine and codeine, and is said to have a slightly sedative effect on the intestinal movements. Its constitutional formula was determined by G. Goldschmiedt—



and it is thus tetramethoxy-benzyl-*iso*-quinoline.

The conversion of this into its *n*-methyl-tetrahydro-compound gives rise to a racemic body, the *d*-variety of which is identical with **laudanosine**, *d*-*n*-methyl-tetrahydro-papaverine (one of the alkaloids occurring in minute quantities in opium)—

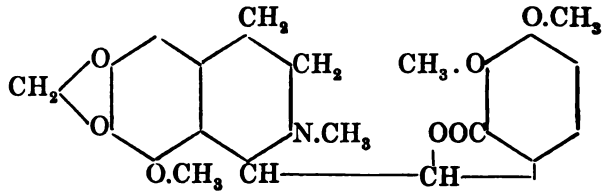


The action of the methyl group, attached to the nitrogen together with the hydrogen atoms, is to convert the mild papaverine into a powerful convulsive poison ranking next to thebaine itself. It

has practically no narcotic action, as the OH group is absent, which serves as an anchoring group to the cells of the cerebrum. The anchoring group for the spinal cord (tetanizing) has not been identified.

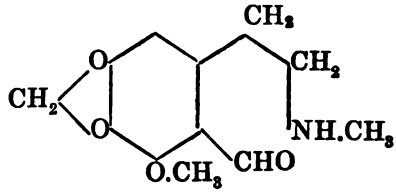
Laudanine, $C_{20}H_{25}NO_4$, which also occurs in two stereo-isomers, has a constitution similar to that of laudanosine, but contains only three methoxy groups, and one hydroxyl, in place of the four methoxy groups contained in that alkaloid. The racemic form can be converted into racemic laudanosine. It should be less powerful a poison than laudanosine, owing to the fact that it has one less methoxy group.

Narcotine, $C_{22}H_{23}NO_7$, closely resembles hydrastine (p. 284) in its chemical structure, it is methoxy-hydrastine—



Its action resembles that of morphine, but is much feebler; it produces a short period of slight exaltation of sensibility, and a little shivering, and then loss of sensation, intoxication, and paralysis. Some loss of sensibility in the eyes and of the nerves to electrical stimulation occurs. The soporific action predominates. It is said that in cats tetanic convulsions precede the stage of narcosis (Mohr), while in man therapeutic doses are only used as an antipyretic. It is also stated to be aphrodisiac.

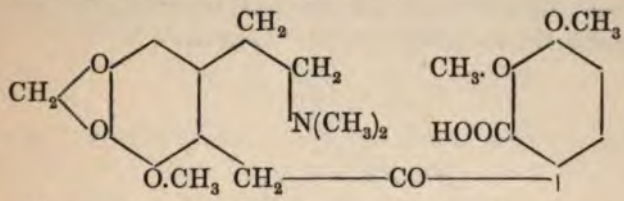
Cotarnine is a decomposition product of narcotine, and its constitution is most probably represented by the formula—



The other product is the non-nitrogenous opianic acid, $C_{10}H_{10}O_5$ (p. 286). It has a slight paralysing action on motor nerves, but not more than other members of the group. Hydro-cotarnine, which contains two less atoms of hydrogen than cotarnine, acts

similarly to codeine, but is less toxic. It is, however, more toxic than morphine.

Narceine, the constitution of which is very probably represented by the formula written below, since it may be obtained by the action of potash on the iodomethylate of narcotine, is said to be inactive in doses of 1 gram or more (Mohr). It is a tertiary base, and a substituted phenyl-benzyl ketone.



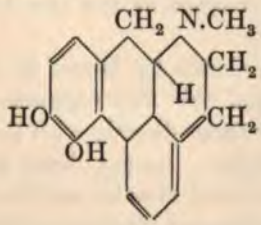
A sodium compound of narceine combined with sodium salicylate has been introduced into pharmacy under the name of **Antispasmin.** Its action resembles that of morphine, but is forty to fifty times weaker.

Narceine-phenyl-hydrazone is said to produce convulsions and respiratory paralysis in doses of ·1 gram per kilo. body-weight.

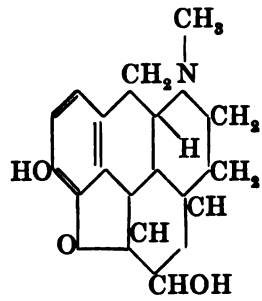
Narceine-ethyl-hydrochloride has recently been introduced, under the name of **Narcyl,** as a remedy for irritable cough. The medicinal dose is ·06 gram.

Apomorphine and Apocodeine.

Dehydrating agents act on morphine in two ways, either by producing condensation products—trimorphine and tetramorphine, &c., or by simply abstracting one molecule of water, giving rise to **apomorphine,** $C_{17}H_{19}NO_3 - H_2O = C_{17}H_{17}NO_2$. This substance can be shown to contain (1) two free hydroxyl groups, and (2) tertiary nitrogen in ring formation; according to Pschorr, it is a derivative of phenanthrene-quinoline—



The position of the hydroxyl in the ring is, however, conjectural. Physiologically, apomorphine is marked by slight narcotic action, but by a considerable degree of excitory power, followed by paralysis of the spinal cord and medulla. The emetic action of morphine is immensely increased. It will be noted that the constitution given above for apomorphine does not resemble that of morphine at all closely. The phenanthrene ring is indeed represented, but not the morpholine. Hence Pschorr has suggested an alternative structure for morphine, the so-called 'pyridine' formula—



This arrangement, however, does not explain certain chemical reactions, e. g. the splitting off of morphol and morphenol from morphine.

It will be seen that, whatever the real structure of morphine may be, apomorphine is not derived from it solely by the abstraction of water, but that its production also involves profound alterations in the ring systems to which the physiological differences must be attributed.

The methylbromide of apomorphine (**Euporphin**) is a less powerful emetic, and has less action on the heart. The removal of the elements of water from codeine gives rise to a substance (apocodeine) having similar physiological reactions, though not so powerful. Its constitution is not definitely known, as it has been found impossible to prove the presence of one free OH group, which by analogy it should contain.

Apocodeine has been shown by Dixon to exert a nicotine-like action on nerve cells, and this fact suggests that the purgative action of opium alkaloids varies directly with their paralysing action on the sympathetic ganglia. Larger doses paralyse motor nerve endings—first those of skeletal muscles and then those of the arterial walls; later those of intestine and bladder, and the accelerator fibres to

the heart are affected. Owing to its action on the ganglionic nerve cells, he has suggested its use as a hypodermic purgative.

Addendum to Alkaloids.

Hordenine,[1] $C_{10}H_{15}ON$, is an alkaloidal body obtained by E. Léger from malt. It is a colourless crystalline substance, dissolving readily in alcohol, chloroform, or ether; Léger[2] has suggested for it the following formula:—

$$1:4\ C_6H_4\begin{matrix}OH\\ CH_2\end{matrix}.CH_2.N\begin{matrix}CH_3\\ CH_3\end{matrix}$$

It forms a number of salts which are readily soluble in water, and whose pharmacological action has been investigated by Camus.[3]

The sulphate is not very toxic, the minimum lethal dose for a dog being ·3 gm. per kilo intravenously. After small doses the vagus is stimulated, and the heart beats more slowly and vigorously; larger doses paralyse the vagus centre. A rise of blood pressure and acceleration of the pulse rate follows on the administration of 1 gram per kilo, to a dog or rabbit *per os*. When a fatal dose is given death occurs from respiratory failure. The action of this body therefore closely resembles that of phenol itself.

[1] *Comp. Rend.*, 1906, **142**, 108. [2] *ib.*, 1906, **143**, 234.
[3] *ib.*, 1906, **142**, 110.

CHAPTER XV

Synthetic Products with Physiological action similar to Cocaine, Atropine, Hydrastis.—Derivatives of Piperidine, Pyrrolidine, Amido- and Oxy-amido-benzoic acid, *para*-Amido-phenol, Guanidine, Tertiary Amyl-alcohol. Halogen and other derivatives. Substitutes for Atropine, Hydrastis.

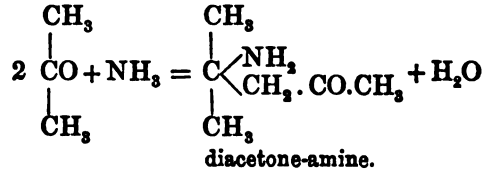
A large number of synthetic products have recently been introduced, the physiological action of which resembles that of various natural alkaloids. Structurally they often closely resemble the bodies they are intended to replace, and in some cases they have certain pharmacological advantages as regards toxicity, rapidity of action, &c. For convenience they will here be grouped according to the alkaloid they are intended to replace, i.e. according to their physiological properties. The various salts of quinine and other bodies introduced as improvements on quinine have already been described, as these are not true substitutes but merely modifications of the original alkaloid.

I. SUBSTITUTES FOR COCAINE.

A. Derivatives of Piperidine and Pyrrolidine.

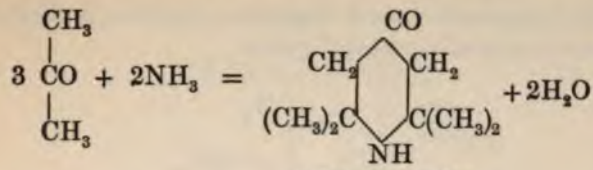
A group of bodies has been introduced as cocaine substitutes, the study of which admirably illustrates the relationship between physiological action and chemical structure, namely, those derived from diacetone-amine, triacetone-amine, and their corresponding alcohols. The first two of these are formed by the action of ammonia on acetone :—

(*a*)



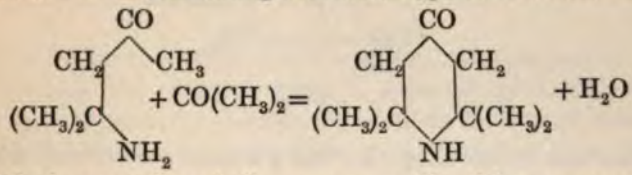
diacetone-amine.

(*b*)

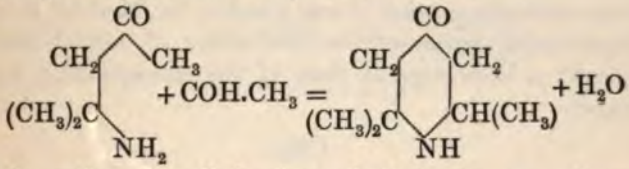


triacetone-amine.

Diacetone-amine, on heating with acetone, gives triacetone-amine—

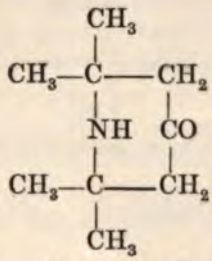


Aldehyde reacts in a similar manner, and by this means a series of bases similar to triacetone-amine may be synthesized. Thus acetaldehyde gives the so-called vinyl-diacetone-amine—

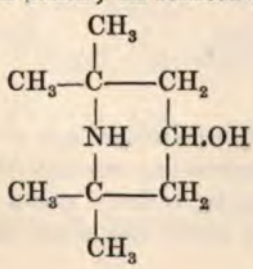


By the action of methylamine and ethylamine on acetone, alkyl derivatives of diacetone-amine are formed.

Triacetone-amine

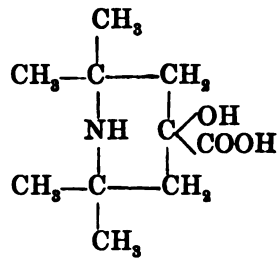


has a powerful curare-like action; its reduced derivative alkamine



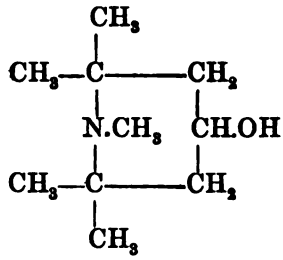
x

and the compounds derived therefrom manifest a similar action; the introduction of a carboxyl group

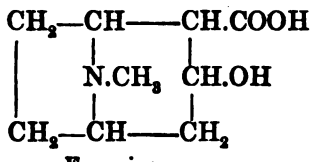


abolishes this action altogether but produces a substance which is more powerfully toxic.

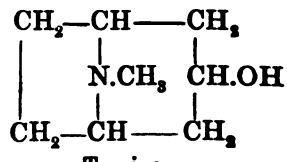
A comparison of the structure of the methyl derivative of triacetone-alkamine with that of tropine and ecgonine reveals a remarkable similarity, so that it was possible for Merling to predict the physiological action of the derivatives of methyl-triacetone-alkamine by a knowledge of those of the corresponding ecgonine compounds.



Triacetone-methyl-alkamine.

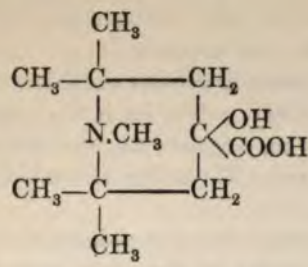


Ecgonine.

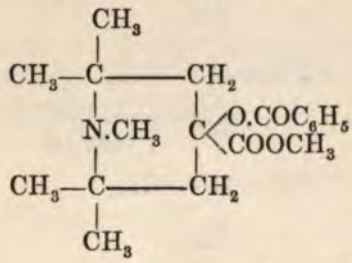


Tropine.

If a carboxyl group is introduced into the first of these derivatives, a body is produced resembling ecgonine still more closely, the main differences being that the carboxyl stands in a different relation to the nitrogen, and the second ring is not closed :—



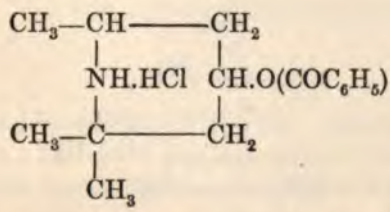
This body is inactive physiologically, like ecgonine. If the hydrogen of the carboxyl group is replaced by methyl and the hydroxyl hydrogen by benzoyl, as is done in the case of cocaine, the following body, known as **Eucaine A** (or α-eucaine), is produced :—



This substance is cheaper than cocaine, and resembles tropacocaine in its action. It does not act on the pupil or contract the arterioles ; it is less toxic, and its solution, unlike that of cocaine, may be sterilized by boiling : on the other hand it has an irritant action on the mucous membrane and is not haemostatic.

Benzoyl-vinyl-diacetone-alkamine has lost some of these disadvantages, and is less toxic than eucaine A, in the proportion of one to four. It is, however, somewhat painful to inject, and it dilates the blood vessels and so promotes bleeding.

The hydrochloride of this substance is known as β-**Eucaine** or **Eucaine B,**



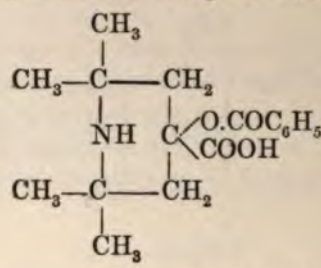
These disadvantages may be overcome by (1) injecting β-eucaine

in normal saline at body temperature, (2) mixing some adrenalin solution with the local anaesthetic.

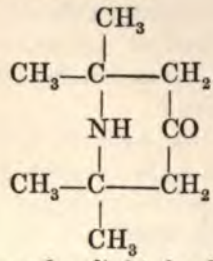
The benzoyl group in eucaine cannot be replaced by acetyl without loss of anaesthetic action (as is the case with cocaine), but other aromatic radicals may replace the benzoyl and leave the local anaesthetic action intact. The amygdalic acid derivative, however, is an exception.

The derivatives of triacetone-alkamine behave similarly to those of the carboxyl derivative, though neither of the parent substances has any local anaesthetic power. The alkyl group in eucaine which replaces the carboxylic hydrogen is not of physiological importance, thus forming a contrast to cocaine.

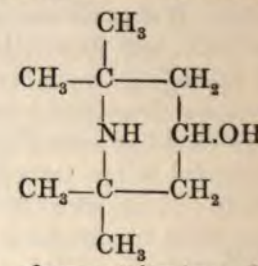
Benzoyl-triacetone-alkamine-carboxyl is a local anaesthetic—



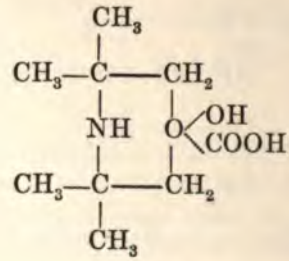
Triacetone-amine,



and triacetone-alkamine

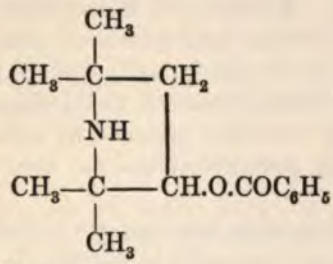


produce only slight local irritation, whereas triacetone-alkamine-carboxyl

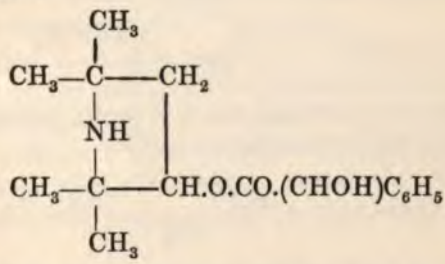


is a powerful local irritant. The carboxyl group seems therefore to be responsible for this effect, which may be much modified by esterification. These esters are, however, two or three times more toxic than the bodies from which they are derived; thus the derivative produced by the substitution of cinnamyl for benzoyl in *α*-eucaine—the methyl-ester of cinnamyl-*n*-methyl-triacetone-alkamine-carboxyl—is three times more toxic than the corresponding cinnamyl-*n*-methyl-triacetone-alkamine. The latter and the corresponding methane compound are among the least toxic bodies of the series; the phenyl and amygdyl derivatives are the most toxic. The alkyl derivatives (ethyl and methyl), though much more toxic than the mother substances, are less so than the aromatic substitution products.

A lower homologue of benzoyl-triacetone-alkamine, benzoyl-*β*-hydroxy-tetramethyl-pyrrolidine has a powerful local anaesthetic action, and is less toxic than *β*-eucaine—



The mandelic acid ester



has a slighter action on the pupil than euphthalmine, which it closely resembles. In fact, a complete series of derivatives can be obtained from the pyrrolidine base corresponding physiologically to those from pyridine, thus illustrating the close relationship between these two bodies.

The general action of the bodies of the eucaine group, when given

in larger doses than those necessary to produce the therapeutic effect, is paralysis of the central nervous system after a more or less marked period of excitation. Those which contain carboxyl (either with or without the ester group) produce increase in reflexes, excitement, general tonic and clonic convulsions, and finally paralysis. The peripheral nervous system is unaffected.

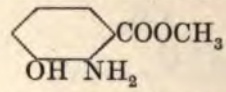
In the bodies without a carboxyl group the excitement is of shorter duration, the general paralysis appears earlier, and is more complete. The motor nerve endings are acted on as in the case of curare, and larger doses paralyse the vagus. Generally speaking, the two classes are typified by the toxic symptoms of α-eucaine and β-eucaine respectively.

B. Derivatives of Amido and Oxyamido Benzoic Acid.

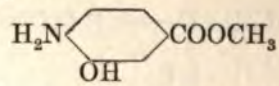
Another series of local anaesthetics has been introduced, of which orthoform is typical. Einhorn and Heintz found that the benzoyl esters of oxy-amido-benzoic acid possessed anaesthetic properties, and on the analogy of cocaine thought that, if the benzoyl group were removed, the anaesthetic action would disappear. This, however, was found not to be the case, and by replacing the benzoyl group more intensely powerful substances were in some instances produced.

Many of these compounds, however, are irritating or painful on injection, and some have but a slight anaesthetic effect.

The methyl ester of *o*-amino-*m*-oxybenzoic acid



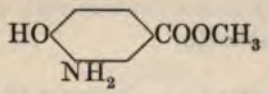
produces an anaesthesia which is hardly perceptible, but the methyl ester of *p*-amido-*m*-oxybenzoic acid



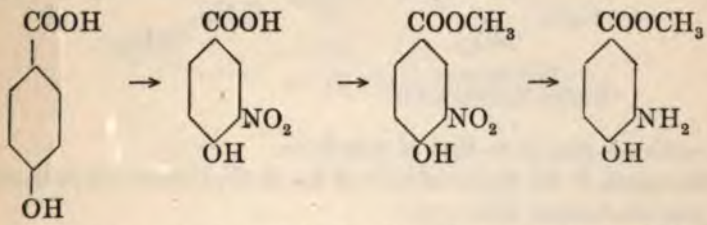
is well known as the local anaesthetic **Orthoform.** This body being very slightly soluble is also but feebly toxic. It is, however, only active when directly applied to the nerve endings, and is useless when applied to the unbroken skin or mucous membrane. Its soluble hydrochloride is not available in practice, owing to the pain produced by its injection. Orthoform has also been observed to give rise to severe dermatitis of an erythematous,

pustular, or even gangrenous type. It is also somewhat expensive (rather more so than morphine hydrochloride).

Orthoform-neu (the new orthoform), the methyl ester of *p*-hydroxy-*m*-amido-benzoic acid,



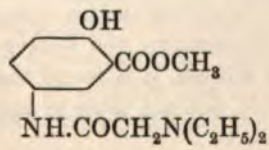
is much cheaper, and equally active physiologically, but except for this it appears to have the same disadvantages as orthoform. Its hydrochloride is soluble, but irritant. It may be obtained from *p*-oxy-benzoic acid, a substance which results from the action of carbon-dioxide on potassium phenate at a temperature of 200–220° C. When this acid is acted upon by dilute nitric acid, *m*-nitro-oxy-benzoic acid results, which is then converted into its methyl ester and reduced :—



A very large number of bodies have been prepared which resemble orthoform, but only a few are of any practical use. It has been found generally that those containing a hydroxyl group in the benzene nucleus, either free or substituted, are all irritant; those which do not exhibit this structure are unirritating.

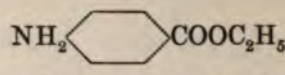
In order to obtain a soluble compound, Einhorn prepared glycocoll derivatives of the amido and carboxy-amido acids of this series. These compounds proved to have anaesthetic properties, but differed from the mother-substance in being strongly basic and easily soluble in water. Their anaesthetic powers do not in any way correspond quantitatively to the substances from which they are derived.

Nirvanine is the methyl ester of diethyl-glycocoll-*m*-amido-*o*-oxy-benzoic acid—

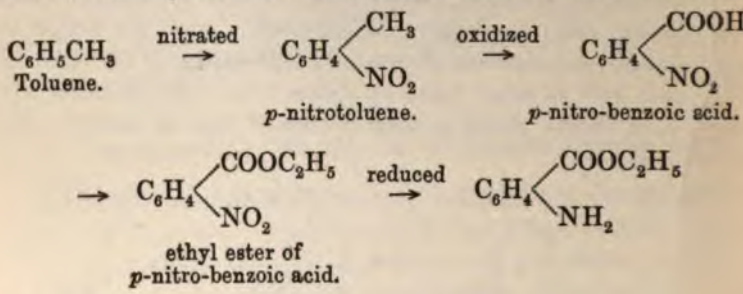


It is less toxic than orthoform, and has also an antiseptic action. It is very soluble in water. It has no action on the unbroken skin; injections produce pain and local oedema, and it is far too irritating for ophthalmic work.

The ethyl ester of *p*-amino-benzoic acid is a local anaesthetic, and is known as **Anaesthesin,**

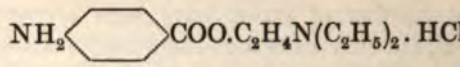


It is obtained by the series of reactions formulated as follows :—



Its action is similar to that of orthoform.

Novocain is the hydrochloride of the diethyl-amino-ethynol ester of *p*-amido-benzoic acid—



It is said to be non-irritant even in strong solutions. It is soluble in one part of water, and the solution may be boiled without decomposition. Its toxicity is slight.

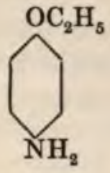
The substances above enumerated, with the possible exception of novocain, are obviously unsuitable for producing surgical anaesthesia. They have, however, been employed with varying success to allay gastric pain, due either to an organic lesion or to functional derangement.

Anaesthesin has also been employed to allay vomiting, when due to causes within the stomach, but seeing that in most of these cases the vomiting serves to remove an irritant and nocuous substance, the field of utility for the drug in this direction appears to be somewhat limited. As illustrating the purely local action of anaesthesin on the gastric mucosa, it is found that it will counteract the effects of tartar emetic, but not those of apomorphine (Reiss).

C. Derivatives of *p*-Amido Phenol.

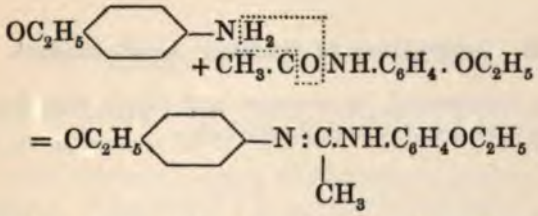
The aniline derivatives, though mainly used as general analgesics, have a slight local anaesthetic action, and in some this property is sufficiently marked to give them a practical value.

Phenetidin,

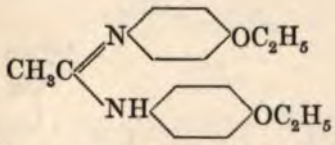


when combined with a second ring, gives rise to the compound known as Holocaine.

Holocaine, the condensation product of *p*-phenetidine and phenacetin,



as employed in practice, is the hydrochloride of *p*-diethoxy-ethenyl-diphenylamine—

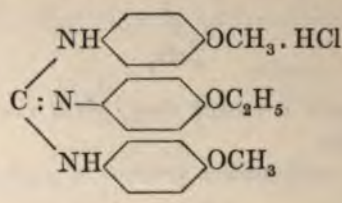


It is more toxic than cocaine, but it produces a rapid anaesthesia. It keeps well, but has the disadvantage of being only slightly soluble. In toxic doses it produces general convulsions. Its practical application has been limited to ophthalmic operations; two or three drops of a 1 per cent. solution produce anaesthesia within one minute, and two or three instillations at intervals of five minutes will render the eye anaesthetic for about forty minutes.

Numerous similar compounds have been tried experimentally, but are found to have no advantage over holocaine. They are, all of them, also antiseptics. It appears that in this series the *ortho* and *para* compounds have equal physiological properties.

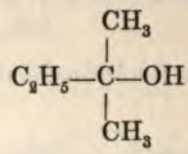
D. Guanidine Derivatives.

The guanidine compounds, of which a large number have been tested, are less toxic than cocaine; they act more promptly and for a longer time, and their solutions are stable. They are, however, irritating; and the solution of the most powerful of the series is decomposed by light. This body, known as **Acoine**, is the hydrochloride of di-*p*-anisyl-monophenetyl-guanidine,

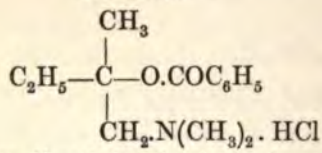


E. Derivatives of Tertiary Amyl Alcohol.

A group represented by stovaine and alypin may be regarded as derivatives of dimethyl-ethyl-carbinol—

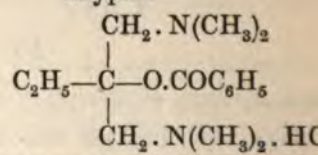


Stovaine:—



or, dimethyl-amino-benzoyl-dimethyl-ethyl-carbinol.

Alypin:—



or, tetra-methyl-diamino-benzoyl-ethyl-dimethyl-carbinol.

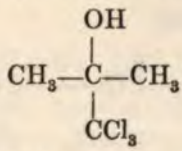
Stovaine differs from cocaine in many important points; whilst it is about as powerful in anaesthetic action it is only half as toxic; it is a vaso-dilator, not a vaso-constrictor, and has a toxic effect on the heart. It has an acid reaction to litmus paper, and is decomposed in the presence of alkalis. It appears to be unsuitable for instillation into the conjunctiva, but may be usefully employed for infiltration anaesthesia. As much as 20 grains have frequently been

given hypodermically without ill-effect, and, in fact, no cases of poisoning are recorded. Its main use hitherto has been in the production of spinal anaesthesia, as little as ·3 cc. of a 10 per cent. solution being sufficient to produce anaesthesia in the legs below the knees. For more extensive anaesthesia as much as 10 cc. may be injected in divided doses.

Alypin, on the other hand, has been mainly employed in ophthalmic work. It possesses for this purpose certain advantages over stovaine. It is not acid, and consequently is compatible with alkaline solutions; it is slightly more active as an anaesthetic, and has no mydriatic action, whereas stovaine in 2 per cent. solution is said to dilate the pupil, though only slightly. Alypin appears, however, to have given rise to local irritation in some cases. It has also been employed to produce lumbar anaesthesia. It may be efficiently sterilized by ten minutes' boiling. It has a slight vaso-dilator action.

F Halogen and other Derivatives.

Two further groups, namely those containing chlorine, and those of the phenol class, may be mentioned. The first is represented in practice by the substance known as **Chloretone (Chloroform Acetone, Aneson).** Chemically it is tertiary trichlorbutyl-alcohol—

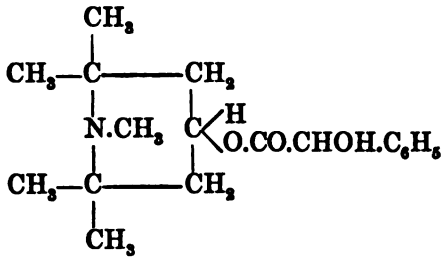


It is used as a sedative and also as an antiseptic; a practical objection to its employment is that the toxic and therapeutic doses are too nearly alike, but it may be employed in small doses to produce local anaesthesia, for dressing wounds, gynaecological applications, &c. Phenol itself, creosote, and guaiacol, are popularly used to inhibit the aching of a tooth, and indeed it appears that all phenols containing at least one free hydroxyl are anaesthetic, though their use is very limited, owing to their caustic action. Their derivatives, such as eugenol acetamide and eugenic acid, do not appear to be powerful anaesthetics, though they are strong antiseptics, and the last-named is said to be non-caustic. Eugenol is 1:3:4-allyl-dioxybenzene, $C_6H_3 . C_3H_5(OH)_2$. It occurs in clove-oil and allspice. Vanillin, $C_6H_3 . (CHO).(OCH_3)(OH)$. 1:3:4; Piperonal

(Heliotropin), $C_6H_3.(CHO).(OCH_2O)$. 1:3:4, are less pronounced local anaesthetics.

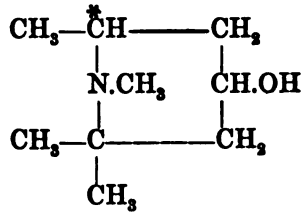
II. SUBSTITUTES FOR ATROPINE.

Not only can bodies having a physiological resemblance to cocaine be derived from triacetone alkamine (see p. 306), but by altering the side-chain a mydriatic substance similar in constitution and action to atropine may be obtained. Atropine, it will be remembered, is the ester of tropic acid and tropine; homatropine the ester with mandelic acid. The mandelic acid ester of methyl-triacetone alkamine is mydriatic—



It will be noted that the hydroxyl is in the *para* position as regards the nitrogen, as in tropine.

Vinyl-diacetone-alkamine,



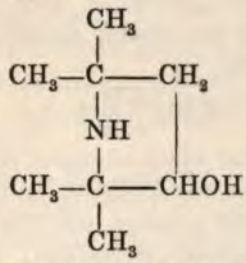
may be treated in a similar manner with like results. Two stereo-isomeric *n*-methyl-vinyl-diacetone-alkamines exist, owing to the presence of an asymmetric carbon atom in the ring, marked with an asterisk on the above formula.

The *α*-mandelic acid derivative is not mydriatic; just as the mandelic acid ester of *ψ*-tropine, isomeric with homatropine, is inactive; the hydrochloride of the *β*-ester is known as **Euphthalmine**. It is easily soluble in water, and has no anaesthetic properties.

Euphthalmine resembles atropine in checking the secretion of the gastric mucosa, and in counteracting the effects of pilocarpine and eserine. In toxic doses it causes in frogs paresis, convulsions, dyspnoea, and death from cardiac failure. It differs from atropine in its retarding action on the pulse rate, due to its action on the vagus centre and the cardiac muscle.

Eumydrine is atropine methyl-nitrate, and is similar in its action to the methyl bromide; it produces a mydriasis of a somewhat enduring nature, and is thus not a suitable substitute for homatropine. **Mydriasine** is the trade name for a preparation of the methyl bromide; the properties of this body have already been described (p. 270).

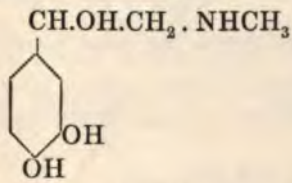
The corresponding mandelic acid ester of pyrrolidine merely destroys the reactivity of the sphincter iridis to light; that of β-hydroxy-tetramethyl-pyrrolidine



is similar to euphthalmine physiologically, but is weaker in mydriatic and toxic action.

III. SUBSTITUTES FOR HYDRASTIS.

The most important body recently introduced into medicine is the extract prepared from the supra-renal glands, and known as **Adrenalin,** supra-renalin, epinephrin, hemisine, &c. The chemical constitution of this body is not absolutely decided, but the balance of evidence is in favour of the formula



Its action physiologically is chiefly on unstriped muscle, which it causes to contract by direct stimulation. Thus Elliott has shown that after the dilator pupillae muscle has been entirely separated

from its nervous connexions for some months it will contract on the application of adrenalin more rapidly and completely than an iris whose nervous supply is intact. It does not act, however, on plain muscle which is not normally innervated by the sympathetic, and thus is without action on the muscles of the bronchioles, and the pulmonary and cerebral blood-vessels. A dose of $\frac{1}{20}$ mgm. intravenously injected in rabbits doubles the general arterial blood pressure, and less than one-millionth of a gram gives a distinct action. In addition to its specific action on unstriped muscle supplied by the sympathetic, adrenalin has certain toxic actions. The $NH.CH_3$ grouping is resistant in the body, and suggests a protoplasmic poison. As a matter of fact, it produces glycosuria and inflammatory changes in the liver and kidneys. It appears also to have a specially toxic action on the cardiac muscle of dogs (Elliott). Death may occur from large doses, with symptoms of collapse, coma, and paralysis of the central nervous system without any increase in blood pressure.

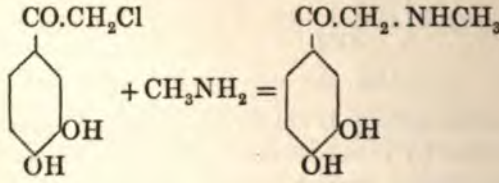
Catechol, $C_6H_4\langle^{OH}_{OH}$ 1:2

the parent-substance from which adrenalin is chemically derived, in doses of about 2 mgms. per kilogram body-weight produces an appreciable rise of arterial pressure, and this is also the case with many of its simpler chemical derivatives; for instance, pyrocatechuic aldehyde, chloracetyl-pyrocatechin, &c. Replacement of the phenolic hydroxyl-hydrogen renders these bodies inactive.

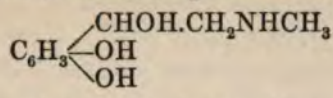
Adrenalone is a ketone obtained by the oxidation of the optically active tribenzene-sulphone derivative of adrenalin. An optically inactive product, which otherwise is apparently identical with the corresponding derivative of the ketone, has been synthesized by the action of methylamine, CH_3NH_2, on

$$C_6H_3\begin{cases}OH & \ldots\ldots 1\\ OH & \ldots\ldots 2\\ CO.CH_2Cl & \ldots 4\end{cases}$$

(a derivative which has much the same physiological activity as catechol).



The synthetic ketone on reduction gives the corresponding alcohol,



which produces as great a physiological reaction as adrenalin, although it is not identical with the natural product, differing chiefly in its optical inactivity. The ketone itself has a vaso-constrictor action, but is hardly more powerful than some of the simpler pyrocatechin derivatives mentioned above.

From synthetic adrenalone a large number of bodies have been prepared which may be grouped into the following classes[1]:—

I. $C_6H_3(OH)_2.CO.CH_2NH_2$.

II. Derivatives of the type $C_6H_3(OH)_2.CO.CH_2NHR$.

(*a*) Where R is in an aliphatic group, e. g. methyl, ethyl, amyl, and heptyl.

(*b*) Where R is a mixed group, e. g. benzyl.

(*c*) Where R is purely aromatic, e. g. phenyl, tolyl, naphthyl.

III. Derivatives of the type $C_6H_3(OH)_2.CO.CH_2.NR_2$, e. g. dimethyl, diamyl.

IV. Derivatives of the ammonium type

$$C_6H_3(OH)_2.CO.CH_2.NR_3OH,$$

e. g. salts of trimethyl, dimethyl-phenyl, &c.

Physiologically, Classes I and II (*a*) all produce a marked rise in arterial pressure in doses of about 1 mgm. per kilogram body-weight, their reduction bases acting similarly to adrenalin. Substances in Class II (*b*) act similarly but less powerfully, and approximate to those in Class II (*c*) which cause a fall of pressure followed by a slight rise. Their reduction products in some cases cause a marked rise of pressure, but on the whole they are not so active as those of the first two groups. Class III is less active than Class II (*a*), but the reduction products are very powerful. Class IV is apparently less active, but only a few members have been tested.

Nicotine, coniine, and other bodies which have a vaso-constrictor action have been dealt with in their place among the alkaloids, and therefore need not be further noticed here; they cannot, moreover, from a practical standpoint, be considered as substitutes for hydrastis.

[1] H. D. Dalkin, *Journ. Physiol.*, xxxii, May, 1905.

CHAPTER XVI

THE GLUCOSIDES.—Sinigrin, Sinalbin, Jalapin, Amygdalin, Coniferin, Phlorizin, Strophanthin, Saponarin, &c. Purgatives derived from Anthraquinone.

THE GLUCOSIDES.

THE **Glucosides** are a class of vegetable substances which on hydrolysis give rise to various aromatic derivatives and sugars—chiefly glucose, but often rhamnose or pentose, and occasionally to a mixture of several sugars.

The name indicates botanical rather than pharmacological or chemical relationships. The common chemical characteristic, the carbohydrate nucleus, is probably of great importance in plant physiology, being the nutritive portion of the molecule; the residual portion is also of importance, and is probably not a mere excretion, as was at one time thought. From the pharmacological point of view, the carbohydrate nucleus appears to increase but not to determine the activity of these bodies. The one exception to the rule that the glucoside is more active than its non-carbohydrate moiety is, according to Fränkel, consolidine, a glucoside obtained from burrage. This body produces paralysis of central origin, and its decomposition product, consolein, is three times more toxic. A number of glucosides can be prepared artificially, though few of these are of pharmacological importance. Van Rijn[1] classifies the naturally occurring glucosides according to the plants from which they are derived. He remarks that, in the present state of our knowledge of the structure of these bodies, a complete chemical classification is not possible; but even were the structure of all glucosides accurately known, a botanical classification would still stand, as, in general, plants of allied species contain similar chemical components.

For the present purpose, however, a chemical classification will be found more convenient. As with the alkaloids, so with the glucosides, only a few out of a large number of natural products are used in medicine, and still fewer have had their chemical structure determined. These may be classified, as was suggested

[1] *Die Glykoside*, 1900.

by Umney, according to the chemical character of the non-glucose portion of the molecule. He divided them into four groups, as ethylene, benzene, styrolene, and anthracene derivatives, and, as far as possible, this classification will be followed. Some glucosides, not in Umney's original list, have been added to his groups, of which the last is the most interesting from a pharmacological point of view.

It will be seen that very little, if anything, is known in this group of the interdependence of constitution and physiological action.

Class I.

The ethylene derivatives include a number of bodies derived from mustard and tropaeolum seeds, characterized by their sharp burning taste, and all allied to, or derived from, mustard oil.

Sinigrin, $C_{10}H_{16}NS_2KO_9 + H_2O$, is the glucoside of black pepper, and is also found in horse-radish root. It is the potassium salt of myronic acid, and probably has the following constitutional formula—

$$\begin{array}{l} O.SO_2OK \\ | \\ C—S.C_6H_{11}O_5 \\ \| \\ N.C_3H_5 \end{array}$$

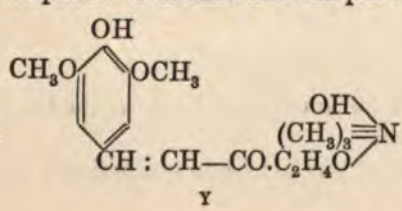
On decomposition it gives rise to allyl-mustard oil, $C_3H_5N:C:S$, glucose, and potassium bisulphate.

Sinalbin, $C_{30}H_{42}N_2S_2O_{15}$, the corresponding glucoside derived from white pepper is

$$\begin{array}{l} O—SO_2OC_{16}H_{24}O_5 \\ | \\ C—S.C_6H_{11}O_5 \\ \| \\ N.CH_2.C_6H_4.OH \end{array}$$

When decomposed, it gives sinalbin-mustard oil, $C_7H_7O.N:C:S$, glucose, and the sulphuric acid ester of sinapin.

Sinapin is a compound of choline and sinapinic acid—



Y

Glycotropaeolin, which has not yet been isolated, is the origin of benzoyl-mustard oil and benzoyl-cyanide, in the seeds of *Tropaeolum majus*. Experiments on its aqueous solution, and the investigation of its derivatives, suggest the constitutional formula—

$$\begin{array}{l} O{-}SO_2OK \\ | \\ C.S.C_6H_{11}O_5 + x\text{Aq} \\ | \\ N.CH_2C_6H_5 \end{array}$$

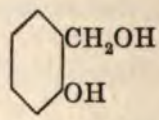
Jalapin (Scammonin), $C_{34}H_{56}O_{16}$, the active principle of Scammony (*Convolvulus scammonia*), is a glucoside, splitting up when heated with dilute acids into glucose and jalapinolic acid, to which Kramer assigns the constitution—

$$\begin{matrix} CH_3 \\ C_2H_5 \end{matrix}\!\!\rangle CHCH.OH.(C_{10}H_{20})COOH$$

This acid has the same composition as the substance obtained from ipomoein (the glucoside from *Ipomoea panduratus*) by heating it with dilute acids, when decomposition into sugar, β-methyl-crotonic acid (?), and ipomeolic acid, $C_{16}H_{32}O_3$, takes place.

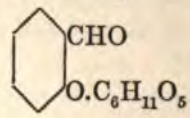
Class II.

The benzene group contains bodies allied to **Salicin**, $C_{13}H_{18}O_7$, a glucoside which is decomposed by dilute acids into glucose and saligenin—



Gaultherin, $C_{14}H_{18}O_8$, the glucoside from *Gaultheria procumbens*, gives salicylic acid methyl ester and glucose, when decomposed by dilute acids.

Helicin, $C_{13}H_{16}O_7$, is the corresponding aldehyde to salicin—



It exists also in an amorphous form (*iso*-helicin), which gives no aldehyde reactions.

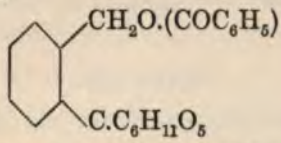
Michael obtained this glucoside synthetically by the action of an

alcoholic solution of aceto-chlorhydrose upon the sodium derivative of salicyl-aldehyde—

$$C_6H_7ClO_5(C_3H_3O)_4 + C_6H_4\begin{cases}OK\\CHO\end{cases} + 4C_2H_5OH$$
$$= C_6H_4\begin{cases}O.C_6H_{11}O_5\\CHO\end{cases} + KCl + 4CH_3COOC_2H_5$$

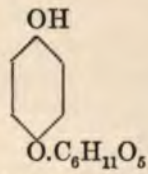
Populin, $C_{20}H_{22}O_8$, which splits up into glucose, benzoic acid, and saligenin, is remarkable in possessing a sweet taste, whereas salicin is bitter, and helicin tasteless.

The conversion of populin into salicin and benzoic acid, and its synthesis from salicin and benzoic anhydride, leads to the following constitutional formula—



The aldehyde, helicin, is a more powerful poison than the corresponding alcohol, saligenin; both are oxidized to salicylic acid in the small intestine; neither liver nor kidney extracts can decompose them (Grisson).

Arbutin, the glucoside found in bearberry and allied plants, has the formula—



It is decomposed by emulsin into glucose and hydroquinone

$$1:4\ C_6H_4\begin{cases}OH\\OH\end{cases}$$

(methyl-hydroquinone is also found, apparently owing to the fact that, besides arbutin, a methyl compound is always present). It is non-poisonous, and is used as a urinary antiseptic and diuretic. In the body the greater part is unchanged, but some hydroquinone is formed, causing the usual greenish tint to appear in the urine. The living cells in muscle and blood appear to have the power of splitting up arbutin, but apparently, as with other glucosides of this group, the main decomposing agency is the putrefactive process of the small intestine. Benzoyl-arbutin (**Cellotropin**) has been tried as a remedy for tuberculosis; it is said to have an injurious action on

the B. Tuberculosis, mainly as a stimulant to the activity of the cells of the host.

Amygdalin, contained in almonds and many other plants (*prunus, pyrus, mespilus,* &c.), is a derivative of the nitrile of mandelic acid,

$$C_6H_5.CH\begin{cases}CN\\O.C_{12}H_{21}O_{10}\end{cases}$$

and the sugar is probably maltose, or a similar di-glucose, which does not contain a free aldehyde group, since amygdalin has no action of Fehling's solution.

Its physiological action depends on its decomposition in the small intestine, with liberation of HCN.

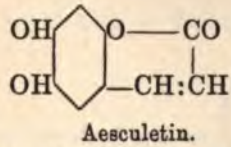
$$C_{20}H_{27}NO_{11} + 2H_2O = 2C_6H_{12}O_6 + \underset{\text{Benzaldehyde.}}{C_6H_5CHO} + \underset{\text{Prussic acid.}}{HCN}$$

Class III.

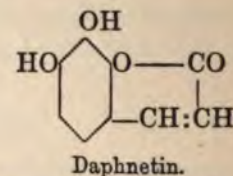
With few exceptions this group does not contain bodies of any great physiological interest.

Styrolene is phenyl-ethylene, $C_6H_5CH:CH_2$.

Aesculin, $C_{15}H_{16}O_9$, a glucoside obtained from the horse-chestnut and other plants, gives, when treated with dilute acids, glucose, and aesculetin, a body which is isomeric with daphnetin (from *Daphne Mezereum*); the constitution of these substances is probably expressed by the formulae—



Aesculetin.



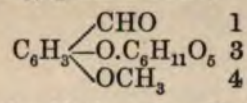
Daphnetin.

Both are dioxy-coumarin. A tincture of the horse-chestnut has been prescribed as an emmenagogue. The dried bark of *Daphne Mezereum* is a gastric stimulant, and externally a rubefacient, but this action is probably due to the volatile oil, and not to the glucoside. The aqueous solution of aesculin has a marked blue fluorescence, which can be seen in the urine fifteen minutes after hypodermic injection. It has been used in lupus as an auxiliary to the Finsen light treatment, apparently its value is due to the fluorescence.

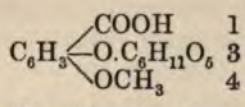
Coniferin, $C_{16}H_{22}O_8$, has the structural formula—

$$C_6H_3\begin{cases}CH:CH.CH_2OH & 1\\O.C_6H_{11}O_5 & 3\\OCH_3 & 4\end{cases}$$

Derivatives of it are (i) gluco-vanillin,



obtained by the careful oxidation of coniferin, and (ii) glucovanillic acid,

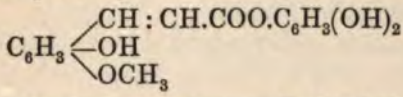


obtained by oxidation of coniferin by means of potassium permanganate. The former is a convulsant poison for some animals, but 10–15 grams have no action on man.

Hesperidin occurs in resinous varieties of *citrus*, on heating with dilute sulphuric acid gives rhamnose, glucose, and hesperetin :—

$$C_{50}H_{60}O_{27} + 3H_2O = \underset{\text{Rhamnose.}}{C_6H_{14}O_6} + 2\ \underset{\text{Glucose.}}{C_6H_{12}O_6} + 2\ \underset{\text{Hesperetin.}}{C_{16}H_{14}O_6}$$

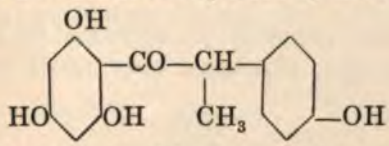
Hesperetin has probably the following constitution :—



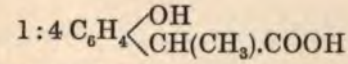
In the alkaloid the hydrogen atoms of the hydroxyl groups are joined to rhamnose and glucose.

Phlorizin is the only glucoside of this group which is interesting from a physiological standpoint. Its action is well known, and is shared in a less degree by phloretin, the body formed when glucose has been split off.

Phloretin has a constitution expressed by the formula—

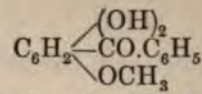


This is based on its decomposition by potash into phloroglucin and phloretinic acid—



In its chemical reactions phloretin is similar to **Cotoin,** a glucoside obtained from coto bark (species undetermined), which has a special action on the intestinal vessels. These are dilated, and thus absorption is favoured. It has no astringent or antiseptic action, but is

largely used in anti-diarrhoeic mixtures in the form of a tincture. The sugar-free nucleus is stated to have the constitution (Schmiedeberg)—



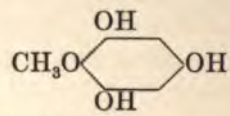
Fortoin is methylene dicotoin, $CH_2(C_{14}H_{11}O_4)_2$; it has not the bitter taste of cotoin, is more powerful in action, and is also bactericidal (*Pharm. J.*, i. 1900, p. 531).

Several substances have been described under the name of **Strophanthin**; two of these are crystalline glucosides obtained from *Strophanthus Kombe*, and the other an amorphous preparation from *Strophanthus hispidus*. Arnaud, and later Kohn and Kulisch, isolated a substance of the composition, $C_{31}H_{48}O_{12}$, from *S. Kombe*. This glucoside has a bitter taste, and its aqueous solution is optically inactive. On hydrolysis it yields strophanthidin, and a sugar or mixture of sugars whose composition has not been determined. Strophanthidin, $C_{19}H_{28}O_4$, or $C_{28}H_{40}O_6$, although a very hygroscopic substance is not soluble in water.

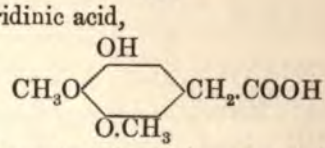
Merck's preparation, which is termed *g*-strophanthin, was isolated from *Strophanthus gratus* by Thoms. The formula $C_{30}H_{46}O_{12}.9\,H_2O$ has been assigned to it; Schedel showed its value in conditions of cardiac weakness. The amorphous strophanthin obtained from the seeds of *Strophanthus hispidus*, is given in much smaller doses than the previous derivative, but whether it is more powerful in its action, or has more toxic properties, has not yet been decided.

In these groups must also be included **Iridin**, $C_{24}H_{25}O_{13}$, a glucoside with a complex structure, obtained from the *Iris florentina* and *Iris versicolor*.

It breaks down primarily on saponification into glucose and irigenine, $C_{18}H_{16}O_8$. This latter body yields iretol (oxymethylphloroglucin),



formic acid, and iridinic acid,

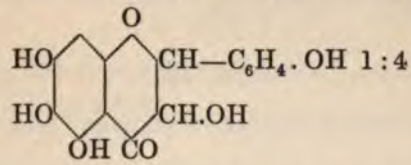


on heating with concentrated solution of potash.

Iridin is a cholagogue purgative.

Saponarin, a glucoside found in *Saponaria officinalis,* and other plants may probably be classed here. With iodine this derivative gives rise to the blue colour characteristic of starch, and hence was formerly regarded as an amorphous variety of that substance.

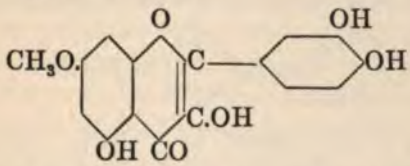
Barger, who has recently investigated this substance, found on hydrolysis that it yielded glucose, a body named saponaretin, and another identical with vitexin, a colouring matter obtained by Perkin from the decomposition of the glucoside of *Vitex littoralis,* and supposed to have a constitution represented by the formula—



Saponaretin may be identical with homovitexin (Perkin).

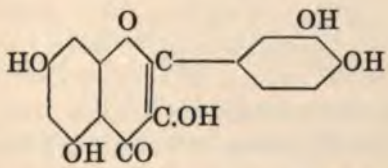
Scoparin may be methoxy-vitexin.

Rhamnetin, the decomposition product of the glucosides of various species of *Rhamnus,* including *R. Purshiana,* is stated to have the following constitution :—



It also is a colouring matter, like Quercitrin $C_{21}H_{22}O_{12}$, which, on hydrolysis, gives rise to quercetin and the carbohydrate rhamnose.

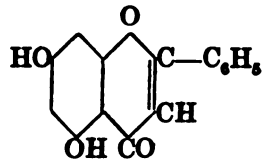
Quercetin



is found combined and free in many varieties of plants, such as the leaves and flowers of the horse-chestnut, and the berries of *Hippophoea rhamnoides.* Perkin and Hummel found an identical pigment in onion rinds. Rhamnetin is mono-diethyl-quercetin, **Fisetin** (from *Rhus Cotinus*) is mono-oxy-quercetin, and a pigment in the

leaves and stems of some species of tamaris is a methyl ether of quercetin—

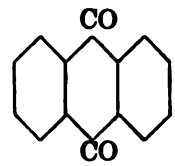
Chrysin,



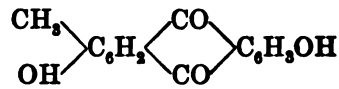
which has three atoms of oxygen less, can be decomposed into phloroglucin, benzoic acid, and acetic acid, just as quercetin yields phloroglucin, protocatechuic acid, and glycolic acid.

Class IV.

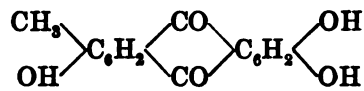
This group contains a number of purgative bodies derived from anthraquinone—



Chrysophanic acid, dioxy-methyl-anthraquinone,



is a purgative principle present in rhubarb. As a glucoside, it occurs as chrysophan, which has not yet been isolated in the same plant. Increase in the hydroxyl groups produces increased purgative action, as in **Emodin,** trioxy-methyl-anthraquinone—



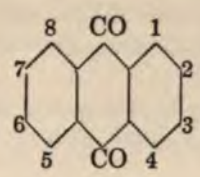
(The orientation of these derivatives is not certain.)

An identical emodin occurs in rhubarb, and combined with rhamnose as a glucoside in frangula bark (Buckthorn); the form obtained from aloes differs slightly.[1] The oxidation product of emodin, aloechrysin, is intermediate physiologically between emodin and chrysophanic acid.

[1] There are fifteen theoretically possible isomers.

Whereas the oxygen appears to increase the intensity of the action, and its position is also of importance, the methyl group appears to be of little importance. Vieth, from the synthetic side, arranged the following table.

The numbers in the formula show the position of the substituting groups :—



Most active, Anthrapurpurin, 1:2:7-trioxy-anthraquinone.
$\frac{1}{2}$ as strong, Flavopurpurin, 1:2:6 „ „
$\frac{1}{3}$ as strong, Anthragallol, 1:2:3 „ „
$\frac{1}{6}$ as strong, Purpur-oxy-anthin, 1:3-dioxy-anthraquinone.
$\frac{1}{10}$ asstrong, Alizarin (Bordeaux), 1:2:3:4-tetraoxy-anthraquinone.
$\frac{1}{20}$ as strong, Purpurin, 1:2:4-trioxy-anthraquinone.

A number of products such as rufigallic acid (hexa-oxy-anthraquinone), acetyl-rufigallic-tetramethyl ether, ordinary alizarin, nitro-purpurin, and cyanin are inactive. Some of the active bodies contain a methyl group and some do not.

The purgative properties have been variously attributed to the anthracene group, to the ketonic groups in anthraquinone, and to the latter in the presence of hydroxyl and aliphatic side-chains. The greater activity of the natural glucosides as purgatives, when compared with their hydrolytic decomposition products, is due to the fact that the latter are too rapidly absorbed from the intestine, and thus lose their laxative effect.

A number of synthetic bodies have been prepared from anthracene —starting from aloin, which has the formula $C_{17}H_{18}O_7 + 1\frac{1}{2}H_2O$, and contains several hydroxyl groups; these have been variously combined in order to produce bodies which, while possessing the purgative action, have not the bitter taste of the parent substance. The compounds should also be more stable and thus more active for reasons already noted.

The methylene radical may replace two hydrogen atoms of hydroxyl groups, and tribromaloin, $C_{17}H_{15}Br_3O_7$, and triacetyl-aloin, $C_{17}H_{15}(C_2H_3O)_3O_7$, have been prepared and found to be active. The last named is also tasteless.

Purgatin or **Purgatol** is a diacetate of anthrapurpurin (1:2:7-

trioxy-anthraquinone), a mild laxative. Marshall states that it irritates the kidneys, and causes pain in the back; the urine is stained red (Dixon).

Exodine is apparently diacetyl-rufigallic-tetramethyl-ether (rufigallic acid is 1:2:3:5:6:7-hexaoxy-anthraquinone); its action is mild. The hexamethyl ether of rufigallic acid has purgative properties, but these are not possessed by acetyl-rufigallic acid, the pentamethyl ether, or the diacetyl-tetramethyl ether of this anthraquinone derivative.

[**Purgen**, not belonging to this group, is phenol-phthalein, and is not absorbed to any considerable extent.]

Saponins.

A series of glucosidic bodies, of which the empirical formulae alone are known, are of great importance from the pharmacological point of view, as among them are many drugs frequently used in practice. These are the saponins, bodies which, for the most part, have the characteristic property of producing a frothy solution with water, and corresponding, with some exceptions, to the general formula $C_nH_{2n-8}O_{10}$.

Various groups have been constructed, according to the number of carbon atoms, but a definite correspondence between these groups and special pharmacological properties has not been made out. The bodies produced by hydrolysis (sapogenins) are usually inert.

Some confusion exists as to the terms employed. Schmiedeberg calls the entire class Sapotoxins, and the hydrolytic decomposition products Saponins. Van Rijn calls the entire class Saponins, applying the term Sapotoxin to some individual members of Kobert's first group. W. E. Dixon notes that the term Sapotoxins should be applied to the 'more active' members of the group, 'but is used somewhat loosely'.

Senegin, quillaia, sapotoxin, saponin, digitonin, quillaiac acid, polygallic acid, sarsa-saponin, and smilax-saponin are among the more important members of the group.

CHAPTER XVII

DEPENDENCE OF TASTE AND ODOUR ON CHEMICAL CONSTITUTION.—*The Organic Dyes.* I. Sternberg's views. Saccharin and its derivatives. Dulcin. II. Odour: Physical and Chemical factors in its production. III. Organic dyes.—Ehrlich's criticisms of Loew's theory of poisons. Picric acid, Aurantia, Chrysoidin, Bismarck brown, Methyl violet, Methylene blue, Phosphorine.

I. TASTE.

INVESTIGATIONS as to the relationships subsisting between the chemical constitution of substances and their effects on the special senses are peculiarly interesting, in that here the application is direct, and such factors as digestion, absorption, elimination, &c., which obscure many points in the physiological action of drugs as a whole, can hardly be considered of preponderating importance. The two special senses of taste and smell may be regarded, so far as our present purpose is concerned, as differing from that of vision in one important particular, namely that the peripheral end organs of taste and smell in the epithelium of the mouth and nose are stimulated directly by certain substances, whereas the rods and cones in the retina are stimulated by etherial vibrations of a certain character and frequency which travel from a distance.

Taking the sensorium generally, a series may be noted, in which the chemical, as opposed to the physical, element in the stimulant becomes more and more pronounced. End organs responding to stimuli of touch, heat and cold, muscular or pressure sense, &c., which are widely distributed over the surface of the body, are absolutely outside the domain of chemical influences. The slow vibrations which are transmuted into nerve impulses by the organs of Corti are also conditioned by physical processes. The distinction between regular and irregular vibrations, however, is well marked.

Passing to the rapid vibrations which are known as light, chemical and physical factors modify the vibrating particles, and hence also the waves set up in the ether, of which only a limited number are perceptible to the eye. But in the case of taste sensations,

owing to the fact that the body in solution is applied directly to the nerve terminations, chemical structure becomes of great importance; and this is also true in the case of smell, where the end organs are directly stimulated by the contact of emanations—of bodies not in solution, but in a gaseous form, as shown by the careful researches of Aitken.

Thus the process by which the end organs of taste and smell are stimulated is more nearly analogous to the process by which a thread (or an animal cell) takes up a dye-stuff than that by which the retina records the impressions of various kinds of light.

Our present knowledge of the subject of intra-molecular vibrations is so slight that nothing more than the mere suggestion can be thrown out that the stimulus in the case of taste and smell is likewise due to some type of vibratory movement, transmitted directly, not indirectly, to the sensitive end organs by the sapid or odorous substance. Several facts in the general relationships which have been shown to exist between chemical structure and taste are at any rate consonant with such a view.

In Mendeleëff's periodic classification of the elements it will be noticed that those possessing a sweet taste are mostly found in the third (boron, aluminium, scandium, yttrium, lanthanum) and fourth (lead, cerium) groups. It is interesting to note that beryllium, which occurs in the second group, but which shows such marked resemblance to the third, should also possess a sweet taste. On the other hand, the bitter elements are found mainly in the second group (magnesium, zinc, cadmium, mercury); while sulphur in the sixth group often gives rise to bitter compounds, and chlorine in the seventh group to sweet ones.

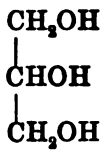
The characteristic taste of acids and bases depends upon their dissociation, the hydrogen ion giving rise to the acid and the hydroxyl to the alkaline taste; consequently the stronger the acid (that is, the greater the degree of dissociation) the more pronounced is the acidic taste. A similar relationship holds good with the alkalis. Organic acids consequently lose their taste on conversion into esters.

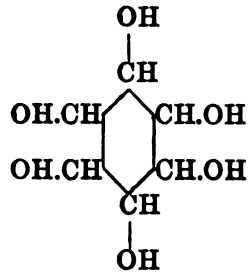
The remaining facts concerning the relationships between taste and smell and chemical constitution are too disjointed for anything like systematic arrangement. They will therefore be grouped under a few main headings, which, while not showing any mutual interdependence, will enable the experimental evidence to be presented in a more orderly manner.

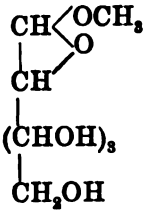
Among organic compounds, substances with very low or with very high molecular weight are usually tasteless.

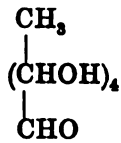
1. Sternberg[1] has pointed out that among organic substances a certain 'harmony' or equilibrium is necessary in order to produce a sweet taste; if this is much disturbed, the sweet taste is lost.

The alkyl and hydroxyl groups must be equal in number, or the former only exceed the latter by one. Thus

glycerin, 

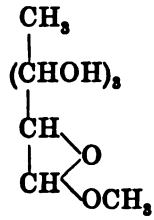
inosite, 

methyl glucoside, 

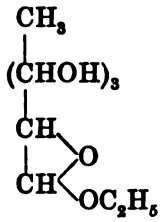
and rhamnose, 

are all sweet; so are the di-saccharides, but the tri- and poly-saccharides are tasteless.

But methyl rhamnoside



is bitter, and the ethyl derivative still more so—



[1] *Geschmack und Geruch*, Dr. Wilhelm Sternberg, and many papers.

2. In the aliphatic series the polyhydric alcohols, oxy-aldehydes, and oxy-ketones are characterized by their sweet taste. In the series from ethyl alcohol to mannite, $C_6H_8(OH)_6$, the taste increases in proportion to the number of hydroxyl groups. Grape sugar, $CH_2OH(CHOH)_4.CHO$, containing an aldehyde group, is sweeter than mannite. Slight alterations in the composition of the sugars completely alter their taste, and the condensation products of the sugars with ketones are all bitter. The replacement of hydroxyl hydrogen by acid radicals converts the sugars into bitter substances, and further replacement produces tasteless derivatives. Although grape sugar is sweet, glycuronic acid, $COOH.(CHOH)_4.CHO$, has the characteristic acid taste.

3. The nitro group does not appear to influence taste in one direction or another. Amyl nitrite and similar compounds, nitrobenzene, 1:2-nitro-phenol are sweet. Trinitro-phenol (picric acid) and dinitro-monochlor-phenol are bitter. Nitro-dichlor-phenol is tasteless.

4. Another fact, connected most probably with molecular equilibrium, is the passage of a sweet substance into a bitter by the replacement of positive alkyl groups by negative phenyl radicals, thus:—

Sweet.	Bitter.
(1) $CH_3.CHOH.CH_2OH$ 1:2-Dioxy-propane.	$C_6H_5.CHOH.CH_2OH$ Phenyl-glycol.
(2) $CH_3.CHOH.CHOH.CH_2OH$ 1:2:3-Trioxy-butane.	$C_6H_5.CHOH.CHOH.CH_2OH$ *a*-phenyl-glycerol.
(3) $CH_2OH.(CHOH)_3.CH.CH.OCH_3$ (O)	$CH_2OH.(CHOH)_3.CH.CH.O.CH_2C_6H_5$ (O)
Methyl-glucoside.	Benzyl-glucoside.

Possibly it is the presence of aromatic radicals in the natural glucosides which accounts in a similar way for their bitter taste.

The introduction of $\cdot CH_2OH$ or chlorine or bromine into the aromatic nucleus of phenyl-glucoside does not diminish the bitter taste, thus:—

phenyl-glucoside, $C_6H_{11}O_5.O.C_6H_5$,

salicin, $C_6H_{11}O_5.O.C_6H_4.CH_2OH$ 1:2,

mono-chlor salicin, $C_6H_{11}O_5.O.C_6H_3\begin{matrix}CH_2OH\\Cl\end{matrix}$

are bitter, but benzoyl-salicin (populin),

$$C_6H_{11}O_5 . O . C_6H_4 . CH_2O(COC_6H_5),$$

is sweet, and the introduction of a second benzoyl group gives rise to a tasteless body.

Tetra-acetyl-chlor-salicin

$$C_6H_7(COCH_3)_4O_5 . O.C_6H_3\begin{matrix}CH_2OH\\Cl\end{matrix}$$

is also tasteless, and so is helicin, the aldehyde of salicin,

$$C_6H_{11}O_5 . O.C_6H_4 . CHO.$$

5. Hydrocarbons, either of aliphatic or aromatic series, are usually tasteless. The introduction of oxygen or nitrogen, however, or of both, under definite conditions may cause the appearance of a substance possessing this quality. Sternberg hence calls them 'Sapiphore' groups.

Positive and negative radicals must be combined in order to produce the effect, negative hydroxyls with positive alkyls, and positive amido groups with negative carboxyls. Thus when NH_2 and COOH groups occur in close proximity in a molecule (i. e. the α position) the effect is more pronounced than when they are separated by carbon atoms (β and γ positions); α-amido-carboxylic acids of the aliphatic series, for instance, are sweet, but β-amido-valerianic acid is only slightly so, and has a bitter after-taste, whereas γ-amido-butyric acid has lost the sweet taste. α-Amido-β-oxy-propionic acid,

$$CH_3 . CH.OH.CH\begin{matrix}NH_2\\COOH,\end{matrix}$$

and α-amido-β-oxy-valerianic acid,

$$CH_3 . CH_2 . CHOH.CH\begin{matrix}NH_2\\COOH,\end{matrix}$$

are quite sweet, whereas α-oxy-β-amido-propionic,

$$CH_3 . CHNH_2 . CH\begin{matrix}OH\\COOH,\end{matrix}$$

is not. In this connexion it is interesting to note that α-pyrrolidine carboxylic acid

$$\begin{matrix}CH_2—CH_2\\|\quad\quad|\\CH_2\quad CH.COOH\\\diagdown\quad\diagup\\NH\end{matrix}$$

has also a sweet taste.

In the aromatic series this does not always hold good, the negative phenyl nucleus playing an important part, as mentioned previously in the case of phenyl-glycerin. Thus phenyl-amido-acetic acid,

$$C_6H_5CH\begin{matrix}NH_2\\COOH\end{matrix},$$

is tasteless, but α-amido-β-phenyl-propionic acid is sweet—

$$C_6H_5.CH_2.CH\begin{matrix}NH_2\\COOH\end{matrix}$$

When the substituents (NH_2 and COOH) are in the ring, Sternberg compares the *ortho* derivatives to the α-aliphatic substances. Thus

$$C_6H_4\begin{matrix}NH_2\\COOH\end{matrix}\ 1:2$$

is sweet, whereas

$$C_6H_4\begin{matrix}NH_2\\COOH\end{matrix}\ 1:4$$

is tasteless. Further, 1:2-amido salicylic acid is slightly sweet, whereas the 1:3 and 1:4 amido acids are tasteless.

The *ortho* sulphonated derivative of benzoic acid,

$$C_6H_4\begin{matrix}SO_2OH\\COOH\end{matrix}\ 1:2,$$

has the characteristic acid taste; the sulphamide,

$$C_6H_4\begin{matrix}SO_2NH_2\\COOH\end{matrix}\ 1:2,$$

is tasteless, but the corresponding inner anhydride, *o*-anhydrosulph-amine-benzoic acid,

$$C_6H_4\begin{matrix}SO_2\\CO\end{matrix}\!\!>\!NH,$$

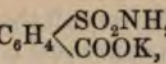
has an intensely sweet taste, and has been introduced under the name of **Saccharin.** It is obtained from toluene by firstly sulphonating at 100° C., which gives the best yield of 1:2-toluene-sulphonic acid,

$$C_6H_4\begin{matrix}SO_2OH\\CH_3\end{matrix}\ 1:2,$$

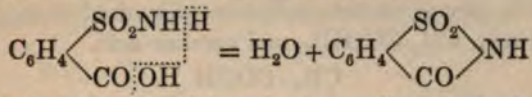
then converting the resulting substance into the sulphochloride by means of phosphorus pentachloride, and this into the amide,

$$C_6H_4\begin{matrix}SO_2NH_2\\CH_3\end{matrix}$$

through the agency of ammonia. *o*-Tolyl-sulphamide is then oxidized by potassium permanganate, and if the solution is kept alkaline the potassium salt of *o*-sulphamine-benzoic acid,



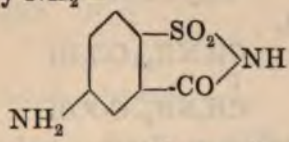
is formed, but when the free acid is liberated by means of a mineral acid, dehydration occurs and saccharin results—



Up to 1891 the commercial saccharin usually contained 40 per cent. of the tasteless 1:4 derivative. One method of separation is based on the differing solubility of these substances in xylene, saccharin being soluble, but the other insoluble.

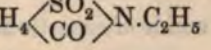
Saccharin passes unchanged through the organism; the sodium salt goes by the name of **Crystallose,** the ammonium is termed **Sucramine.**

Saccharin still retains its sweet taste when a hydrogen atom of nucleus is replaced by NH_2—



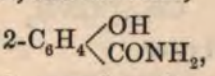
but a corresponding replacement by a nitro group gives rise to a substance with bitter taste.

The replacement of the imide hydrogen by the ethyl group

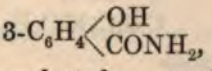


results in a tasteless substance.

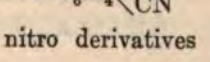
6. Salicylic acid is sweet, and its amide,



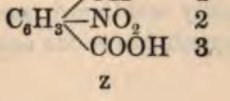
is tasteless; but although *m*-oxybenzoic acid is also sweet, its amide,



is bitter; its dehydration product, however, the nitrile



is sweet. Among the nitro derivatives of *m*-oxybenzoic only one, viz.



is sweet, the others are tasteless; all the dinitro-*m*-oxybenzoic acids are also tasteless, but the trinitro acid is bitter.

The dioxybenzoic acids are tasteless.

7. The presence of two carboxyl groups in the molecule and the effect of NH_2 groups on taste is illustrated by the following facts:—

Malonic acid, $CH_2(COOH)_2$, and succinic acid

$$\begin{array}{l} CH_2.COOH \\ | \\ CH_2.COOH \end{array}$$

have the ordinary acid taste; methyl-amido-malonic acid

$$CH_3.C(NH_2)\begin{array}{l}\diagup COOH \\ \diagdown COOH\end{array}$$

is sour, and so is aspartic acid—

$$\begin{array}{l} CHNH_2.COOH \\ | \\ CH_2.COOH \end{array}$$

Diamido-succinic acid,

$$\begin{array}{l} CH.NH_2.COOH \\ | \\ CH.NH_2.COOH \end{array}$$

a substance which is only very slightly soluble in water, is tasteless. Dextro-glutaminic acid

$$CH_2\begin{array}{l}\diagup CH_2.COOH \\ \diagdown CH.NH_2.COOH\end{array}$$

is sweet, and so is the amide of aspartic acid, i. e. dextro-asparagin,

$$\begin{array}{l} CH.NH_2.COOH \\ | \\ CH_2.CONH_2 \end{array}$$

Imido-succinic-ethyl ester

$$\begin{array}{l} CH.COOH \\ | \quad \rangle NH \\ CH.COOC_2H_5 \end{array}$$

is bitter, whereas its amide

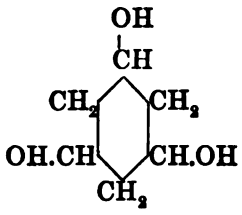
$$\begin{array}{l} CH.CONH_2 \\ | \quad \rangle NH \\ CH.COOC_2H_5 \end{array}$$

is sweet.

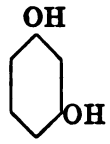
8. The effects of stereochemical influences upon the sense of taste have been previously mentioned (see p. 53). This influence is but slight, or at all events has so far only been noticed in a few

cases. *Dextro*-asparagin is sweet, the *laevo* modification is not; both *d*- and *l*-aspartic acids have the same taste. *Dextro*-glutaminic has a sweet taste, the *laevo* form is tasteless.

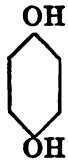
9. The symmetry of aromatic hydroxyl derivatives appears to be of importance in determining the sweet taste, thus:



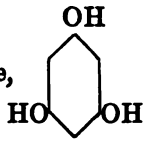
Trioxy-methylene, phloroglucite,



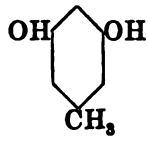
Resorcin,



Hydroquinone,

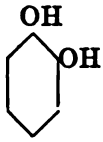


Phloroglucin,

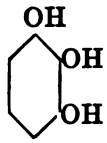


Orcinol,

are all more or less sweet, whereas



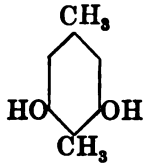
Pyrocatechin, and



Pyrogallol

are bitter, and

β-orcin



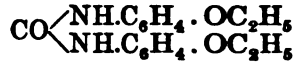
is tasteless, and the previously-mentioned orcinol is the only sweet dioxy-toluene.

10. The effect of the symmetry of the molecule is also seen in the substituted ureas; many of the unsymmetrical have a sweet taste, whereas the symmetrical are tasteless, thus:

α-*α*-dimethyl urea.
Sweet.

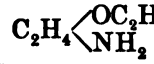
α-*β*-dimethyl urea.
Tasteless.

1 : 4-phenetol carbamide (Dulcin). Sweet.



Di-*p*-phenetol carbamide. Tasteless.

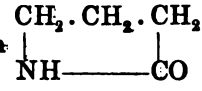
Dulcin, or **Sucrol**, breaks down in the organism, giving rise to the toxic substance phenetidin,

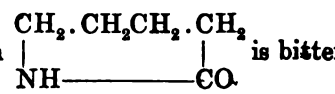


consequently its physiological action is similar to that of the phenacetin derivatives.

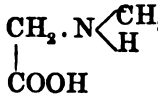
11. The conversion of chain into cyclic derivatives also affects taste. Thus:

γ-amido-butyric acid, $NH_2.CH_2.CH_2.CH_2.COOH$, is tasteless,

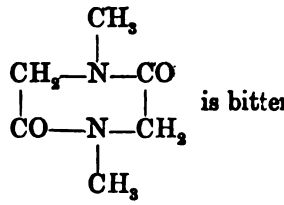
pyrrolidon  is bitter,

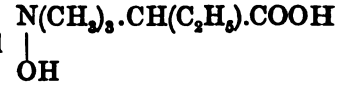
δ-amido-valerianic acid  is tasteless,

oxy-piperidon is bitter.

Sarcosin  is slightly sweet,

whereas its anhydride

 is bitter.

Trimethyl-amido-butyric acid  is sweet,

the anhydride bitter.

Sternberg ascribes the bitter taste of the alkaloids to their cyclic constitution.

II. ODOUR.

Our knowledge of the correlation of odour and structure has been mainly acquired for the purpose of producing synthetic perfumes, an industry largely carried on in Germany and France. In the short sketch which follows the authors are mainly indebted to the works of Georg Cohn[1] and Zwaardemaker[2], the former from the chemical, and the latter from the physiological side.

The most necessary condition for the production of an odorous substance is volatility, since it is found that bodies of low volatility —generally associated with high molecular weight—have no effect on the olfactory organs. But the molecular magnitude must fall within certain limits; frequently those with low molecular weight —such as the volatile aldehydes of the aliphatic series—have unpleasant odours, whereas the higher members have none at all; between these limits lie citral and citronellal (p. 344), which are typical scents, and the aromatic aldehydes, of higher molecular weight, which also have pleasant odours.

Some importance must also be ascribed to the concentration of the odorous substance and most probably to the nature of the solvent. Such substances as vanillin, piperonal, cumarin, and ionone, have a very different odour when in strong solution to that which they possess when much diluted. The natural essential oils used in perfumery owe their pleasant odour to several constituents, and small variation in the concentration of one may bring about great alterations in the odour of the oil itself. It is generally stated that artificial benzaldehyde cannot be used for the more expensive varieties of scent, owing to the impossibility of freeing it from minute traces of impurities. Phenylacetic acid and β-naphthylamine have no odour in the crystalline condition, but smell disagreeably when in solution.

This property has been compared to the variation in colour sometimes observed when a solid dye-stuff is dissolved in water, and a further similarity has been noted between the way in which odours adhere to certain bodies like paper, woven materials, &c., and the process of dyeing.

1. The chemical constitution of a substance is clearly of primary importance in determining its odour, but at present little is known of the general correlation between these two. Following the analogy with the dyes, certain '*Osmophore*' groups have been described, such

[1] *Die Riechstoffe*, 1904. [2] *Physiologie des Geruchs*, 1895.

as hydroxyl (OH), aldehyde (CHO), ketone (.CO.), ether (.O.), nitrile (CN), nitro (NO_2), azoimide (N_3), which may condition odour in various bodies previously odourless, and such groups may obviously give rise to substances of pleasant or unpleasant odour. But a classification on the basis of the osmophores is impossible in the present state of our knowledge. Equally impossible is a classification based on the character of the odour, as there are no words in any language by which odours may be described, the only terms in use being those which point a similarity to some other odour, such as 'camphoraceous', 'vinous', &c.

2. Two or more osmophore groups may be present in the same body, or one may often replace another without materially altering the odour; thus benzaldehyde, nitrobenzene, benzonitrile, phenyl-azoimide, have all a very similar smell. The introduction of several substituent groups, however, leading to an increase in the molecular weight, may account for the observed diminution in the intensity of the odour of the resulting derivative.

3. Homologous derivatives usually have a similar smell; this is noticed in the case of the methyl and ethyl esters of salicylic acid, or the methyl and ethyl ethers of β-naphthol, or the corresponding di-derivatives of hydroquinone.

But the ethyl group in the esters and ethers may lead to a striking diminution in the odour, whereas the methyl derivatives are scented (compare p. 49). Thus the ethyl ester of anthranilic acid,

$$1:2\ C_6H_4\begin{cases}NH_2\\COOC_2H_5,\end{cases}$$

has only a slight smell; the *iso*-butyl ester has none, but the methyl ester has the odour of orange blossoms.

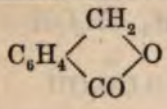
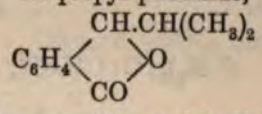
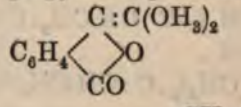
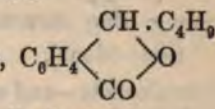
In the aromatic series the entrance of a methyl group into the ring does not cause much alteration in the odour; thus nitro-benzene and nitro-toluene are very similar, and methyl-vanillin, methyl-cumarin, smell very like the substances from which they are derived. Radicals rich in carbon have a considerable influence on odour, as illustrated in the table on the next page.

The amyl radical appears to have a special function, as it produces a uniform odour in the bodies into which it is introduced, e. g. amyl-alcohol, amyl-methyl-ketone, amyl- and diamyl-aniline.

4. The halogens only influence odour when introduced into the side-chains, and not when substituted in the nucleus of aromatic derivatives; thus brom-β-naphthol-methyl-ether and the chlorinated benzaldehydes have a similar smell to the parent substances.

5. Phenols and phenol ethers have characteristic odours, and those with olefine substituents, especially the allyl or propenyl groups, are found in several volatile oils. The carboxyl group destroys the odour of alcoholic and phenolic substances.

6. Nitrogen-containing radicals play an important part in determining odour, and for this purpose the nitro group is of more importance than the nitrile.

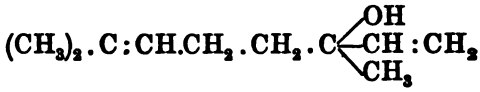
Phthalide has no smell. 	*iso*-propyl-phthalide,  *iso*-propylidene-phthalide,  butyl-phthalide,  all smell of celery.
Phenyl-acetylene has an unpleasant smell. $C_6H_5.C:CH$	1 : 4-tolyl-acetylene, $CH_3.C_6H_4.C:CH$, 1 : 4-ethyl-phenyl-acetylene, $C_2H_5.C_6H_4.C:CH$, both smell of anise. 1 : 4-*iso*-propyl-phenyl-acetylene, $(CH_3)_2CH.C_6H_4.C:CH$, *s*-trimethyl-phenyl-acetylene, $(CH_3)_3C_6H_2.C:CH$, have a pleasant etherial smell.

iso-Nitriles generally have extremely disagreeable odours. The higher homologues of trinitro-benzene smell of musk. Methyl-benzoate has the characteristic slight smell of so many of the aromatic esters, whereas the 1 : 4-amido derivative smells of orange blossom. In the series of nitro derivatives smelling of musk a nitro group may be replaced by the azoimide without altering the odour of the original substance.

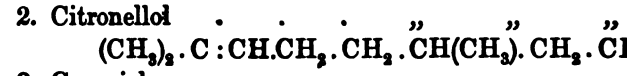
7. It is among the higher alcohols and ketones, and especially the aldehydes, that the majority of substances used in perfumery is to be found. The following list contains a few typical examples of each class. The isolation and identification of such substances from the essential oils and their artificial production, or the synthesis of closely allied derivatives, has been developed with great success during the last twenty-five years, and has resulted in an industry of considerable importance:—

Alcohols:

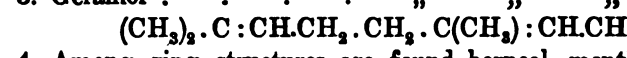
1. Linalool . . . . odour resembles that of mayflower



2. Citronellol . . . . „ „ „ roses



3. Geraniol . . . . „ „ „ roses

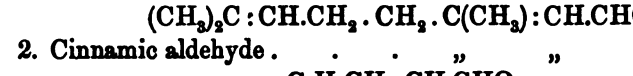


4. Among ring structures are found borneol, menthol, terpineol (lilac odour).

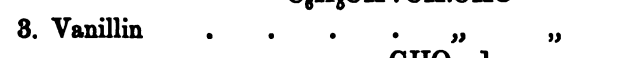
These alcohols—and so far only those with more than eight carbon atoms have been found in volatile oils—may be converted into esters (see p. 122) and variations in odour obtained. Thus the linalool and geraniol esters of acetic acid have an odour of oil of bergamot. The esters of borneol all possess an odour similar to the acetate, the intensity of which diminishes with an increase in the molecular weight of the acid. The acetate of *l*-borneol is present in oil of hemlock, valerian, kesso, &c.

Aldehydes:

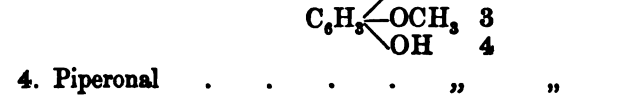
1. Citral or geranial . . . odour resembles that of lemons



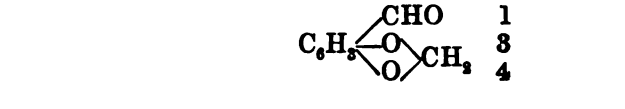
2. Cinnamic aldehyde . . . „ „ „ cinnamon



3. Vanillin . . . . „ „ „ vanilla



4. Piperonal . . . . „ „ „ heliotrope



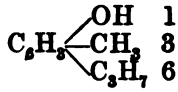
Ketones:

1. Methyl-ethyl-acetone . . odour resembles that of peppermint

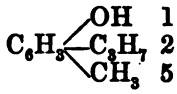
2. Various derivatives of cyclo-hexanone, e.g. pulegone „
3. Camphor, fenchone, carvone (odour of caraway)
4. Ionone . . . odour resembles that of fresh violets
5. Various substitution products of acetophenone, $C_6H_5.CO.CH_3$.

Phenols and Phenol-ethers:

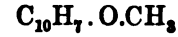
1. Carvacrol . . . . . odour resembles that of thyme



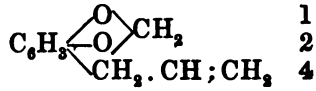
2. Thymol . . . . . „ „ thyme



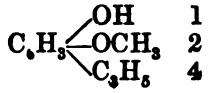
3. β-naphthol-methyl ether . . „ oil of neroli



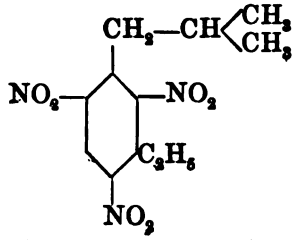
4. Safrol . . . . . „ oil of sassafras



5. Eugenol . . . . . „ oil of cloves



8. Isomeric relationships naturally play an important part in conditioning odour, as they do with regard to other physical characteristics of organic compounds. Thus *iso*-vanillin is scentless, and in the artificial musks—e.g. in trinitro-ψ-butyl-ethyl-benzol,



and in many similar derivatives having the same odour, the three

nitro groups must be symmetrically placed, otherwise this characteristic is lost.

The 1:2 and 1:4 (but seldom the 1:3) positions in the benzene nucleus are substituted in many of the artificial scents. Thus 1:4-methoxy-acetophenone, $CH_3.CO.C_6H_4.OCH_3$, has a pleasant smell; the 1:3 isomer is without scent. 1:2-amido-acetophenone,

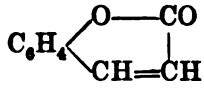
1:2-amido-benzaldehyde,

and 1:2-nitro-phenol have strong odours, whereas the corresponding 1:3 and 1:4 derivatives have none. In this connexion it may be mentioned that although salicyl (*ortho* derivative) and anis-aldehydes (*para*) both occur in nature, neither the corresponding *m*-oxy-benzaldehyde nor its derivatives are found.

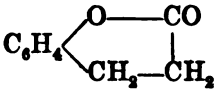
9. Reduction may alter a scent, but does not render it disagreeable, as seen in the following cases. Cinnamic aldehyde,

$$C_6H_5CH:CH.CHO,$$

smells of cinnamon. The reduced derivative, $C_6H_5.CH_2.CH_2.CHO$, has a most characteristic odour of lilac and jasmine. Coumarin



has the odour of woodruff, also noticeable in melilotin—



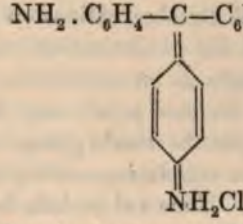
10. Unsaturated substances generally have powerful odours. Triply-linked carbon systems are frequently associated with unpleasant odours, thus phenyl-propiol-aldehyde, $C_6H_5C:C.CHO$, and 1:2-nitro-phenyl-acetylene, $NO_2.C_6H_4.C:CH$, are most disagreeable. This may be contrasted with the effect of the double bond, which usually gives rise to bodies with pleasant smells; compare styrene, $C_6H_5CH:CH_2$, which is found in storax oil, and various other instances which have been previously given.

III. THE ORGANIC DYES.

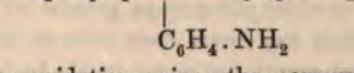
Spectroscopic investigations have shown that no open-chain hydrocarbon causes selective absorption, but that benzene and allied hydrocarbons are characterized by selective absorption of the most refrangible rays, and are thereby differentiated from all other classes.

Consequently, it may be stated that benzene has 'invisible' colour (Hartley) which will become visible when the rate of vibration of the molecule is so slackened, that it will be possible for the molecule to absorb rays having an oscillation frequency occurring within the limits of visibility. Phenol, C_6H_5OH, is 'invisibly' coloured; it shows selective absorption in the ultra violet region, but the replacement of these hydrogen atoms by three nitro groups gives the yellow picric acid. The mere fact, then, that an aromatic substance is coloured or has dyeing properties does not necessarily mean that it will in consequence show any novel pharmacological action.

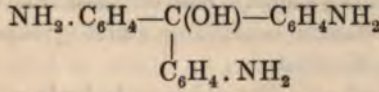
The reduction of a dye-stuff results in the formation of the so-called 'leuco' compound. For instance, pararosaniline



becomes the colourless leuco-pararosaniline—



This derivative, on oxidation, gives the corresponding colourless carbinol, the base of the dye,



which on treatment with hydrochloric acid gives the dye itself.

In general, the accumulation of carbon atoms deepens the tint, as also does the introduction of substituting groups. Thus rosaniline is red, and as the hydrogen atoms of the NH_2 groups are replaced

by methyl radicals, the colour passes from red to violet-red, and in hexa-methyl rosaniline becomes violet-blue. The replacement of hydrogen atoms by ethyl or phenyl groups intensifies this effect. Hexa-ethyl rosaniline is violet with a blue nuance, and the triphenyl substitution product is blue.

Allusion has already been made (p. 22) to the auxochrome groups described by Witt. These are of two kinds, basic and acid, so that from each chromogen two series of analogous dyes may often be obtained, thus :—

Acid Dyes.	**Basic Dyes.**
Auxochrome (OH).	Auxochrome (NH_2).
Oxy-azo-benzene.	Amido-azo-benzene.
Dioxy-azo-benzene.	Diamido-azo-benzene.
Rosolic acid.	Rosaniline.
Thionol.	Thionoline.
Aposafranone.	Aposafranine.

The introduction of more than one acid or basic auxochrome group will, to some extent, tend to deepen the intensity of the colour.

Largely on the grounds of his observations on the action of dyestuffs Ehrlich has criticized the 'substitution' theory of Loew, to which allusion has been made in an earlier chapter (p. 17). The evidence he has collected on this point may be summarized as follows[1] :—In some basic dyes the amido group, or groups, undergo interaction with substances containing aldehyde radicals, and a change of colour is produced. Thus red fuchsin becomes violet when treated with an aldehyde. Now, in the case of the substituting poisons, Loew supposed that an interaction took place between these and amido or aldehyde groups present in the living protoplasm. But Ehrlich has never been able to observe that colour changes of the type mentioned occur in the body, either with this basic dye which reacts with aldehyde groups, or with certain other dyes (e.g. Kehrmann's azonium base obtained from safranine) which interact with substances containing amido groups, causing characteristic changes of colour.

Other bodies, such as anilin and benzaldehyde, which very readily condense to benzylidene-anilin, have also been employed, but no derivative of either anilin and an aldehyde-containing substance, or

[1] *Studies in Immunity*, 1906, chap. xxxiv.

of benzaldehyde and an amido group, has ever been extracted from the tissues.

Ehrlich has also employed the aromatic dyes to elucidate the distribution of poisons and drugs in the animal body, or, in other words, to throw light on the selective action of cells. Thus he shows that the brown staining with *para*-phenylene-diamine, which is most marked round the central tendon of the diaphragm, and the muscles of the eye, larynx, and tongue, is due to the more copious blood supply of these muscles, that is, to the presence of an abundance of oxygen. Similarly, in these situations the motor nerve endings were more intensely stained with methylene blue.

From observations of this character Ehrlich deduces the hypothesis that the various cells of the body take up different chemical substances in a greater or less degree according to their 'chemical environment':—absence or presence of oxygen, alkaline or acid reaction, &c. Thus a nerve ending, if in a neutral or acid environment, will take up the dye alizarin, but when the surrounding reaction is alkaline it is stained by quite a different substance, namely, methylene blue.

It is possible to modify the distribution of a dye-stuff by the addition of other substances; thus the staining of the nerve endings by means of methylene blue, which occurs *intra vitam*, may be prevented by the addition of the soluble acid dye called orange green. The latter, that is, has a stronger affinity for the methylene blue than the nerve endings possess. On this principle is compounded the well-known 'Triacid' stain.

The introduction of a second body may also render a dye active in the tissues; thus Bismarck brown does not stain peripheral nerve endings (e. g. taste buds) in the frog, but the addition of methylene blue causes the nerve endings to take a double colour. In permanent preparations the blue quickly fades, and the brown stain only remains. Ehrlich believes that this principle underlies many of the 'abnormal actions of drugs, especially in inherited or acquired hyper-sensitiveness'.

Besides these somewhat theoretical results, observations on the physiological action of the organic dye-stuffs have also, of recent years, begun to lead to results of practical value; and it is quite possible that important developments in therapeutics may result from a further study of these derivatives. Many possess a remarkable bactericidal action, but it has not as yet proved possible to employ them against ordinary bacterial infections. The parasitic

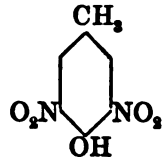
trypanosomes have, however, been shown to be markedly influenced both in experimental animals and in man by treatment with certain dye-stuffs, such as malachite green G (see p. 354), and trypan red (see p. 352). These bodies are thought to act by favouring the development of immunizing substances within the organism.

Malachite green has also been employed by F. Loeffler for separating colonies of B. coli and B. typhi abdominalis; the growth of the former organism was prevented by an admixture of this dye with the culture medium, the colonies of the latter remaining unaffected.

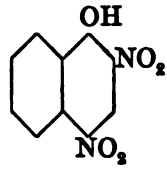
Class I.

Nitro Derivatives of the Phenols.

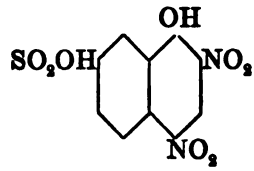
Picric Acid, $C_6H_2(NO_2)_3OH$, and **Dinitro-cresol**—



The introduction of the nitro group into phenolic substances increases the antiseptic and toxic action. Both are powerful blood poisons, renal irritants, and respiratory depressants, especially the latter, possibly owing to its greater solubility. The group of naphthol nitro-derivatives includes Martius yellow,



which is similar in its action to dinitro-cresol. The introduction of a sulphonic grouping, resulting in the formation of dinitro-1-naphthol-7-sulphonic acid,



naphthol yellow S, has the usual effect of destroying the toxicity.

Aurantia or **Kaiser Yellow** is the ammonium or sodium salt of hexa-nitro-diphenylamine,

$$NH\begin{cases}C_6H_2(NO_3)_3\\C_6H_2(NO_3)_3\end{cases}$$

and is stated to have toxic properties.

Class II.

Azo - Dyes.

The azo-dyes are a class of substances which contain as chromophore the group .N:N. As previously mentioned, azo-benzene itself, $C_6H_5.N:N.C_6H_5$, although possessing a red colour, is not a dye-stuff; by the entrance of auxochrome groups, such as hydroxyl and amido, the colouring power appears, and the shade is modified. The simplest azo-dyes, like most simple dyes, are yellow, and their tint is dependent firstly on the nature of the auxochrome group, and secondly on that of the carbon complex. They may be made to pass through red to violet, and in some cases to brown. Blue azo-dyes have so far only been obtained from those substances containing several azo-groups in the molecule. Those containing the benzene nucleus are yellow, orange or brown; those containing the naphthalene, red; by the entrance of several of the latter nuclei, violet-blue or black dyes are produced.

As a general rule their technical preparation is extremely easy.

Aniline, for instance, is diazotized in the usual way, and when the solution is added to an alkaline solution of the phenol or its sulphonate, oxy-azo-benzene or **Tropaeolin .Y.** is formed—

1. $C_6H_5NH_2 \rightarrow C_6H_5N:NCl.$
2. $C_6H_5N:N.Cl + C_6H_5ONa = NaCl + C_6H_5N:N.C_6H_4OH.$

In this reaction phenol may be replaced by resorcin, α- or β-naphthol, their various sulphonates, or salicylic acid. Sulphanilic acid and benzidine

$$\begin{matrix}C_6H_4NH_2\\|\\C_6H_4NH_2\end{matrix}$$

may be used in place of aniline, and consequently a large number of dye-stuffs can be obtained.

The combination of diazo bodies with amines, as a rule, is not so easy. Some, such as 1:3-phenylene-diamine,

$$C_6H_4\begin{cases}NH_2\\NH_2\end{cases}$$

combine directly in neutral aqueous solution; thus chrysoidin is obtained by mixing equivalent solutions of diazo-benzene chloride and 1:3-phenylene-diamine,

$$C_6H_5.N:N.Cl + C_6H_4\begin{matrix}NH_2\\NH_2\end{matrix} = C_6H_5N:N.C_3H_2\begin{matrix}NH_2\\NH_2\end{matrix} + HCl.$$

But in other cases, as with diphenylamine, solution in methylated spirits and treatment with a strong solution of the diazo derivative is requisite.

The azo-dyes, containing a sulphonic acid group, are, as might be expected, but slightly toxic substances,[1] and are used for colouring wines (Rouge soluble, Bordeaux B, Ponceau R, Orange 1, Jaune solide). Those without such groups have also, as a rule, but slight poisonous properties.

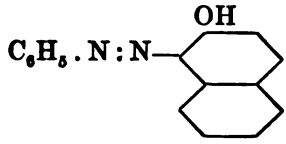
Chrysoidin $C_6H_5.N:N.C_6H_3\begin{matrix}NH_2\\NH_2\end{matrix}.HCl$

produces slight albuminuria and a marked reduction of body-weight. In very dilute solution it agglutinates cholera and other vibrios. It has antiseptic properties, but no specific action.

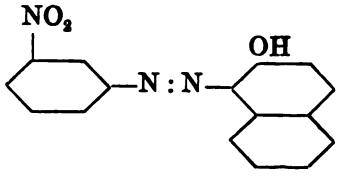
Bismarck brown $C_6H_4\begin{matrix}NH_2\\N:N.C_6H_3\end{matrix}\begin{matrix}NH_2\\NH_2\end{matrix}$

has toxic properties.

Sudan 1

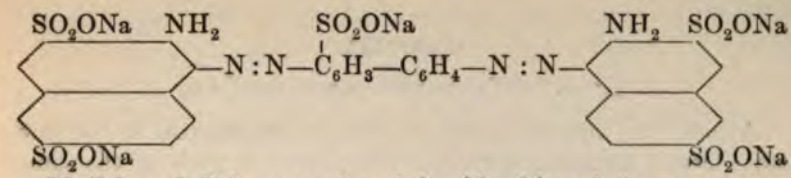


produces slight albuminuria, but the *m*-nitro compound is non-toxic.



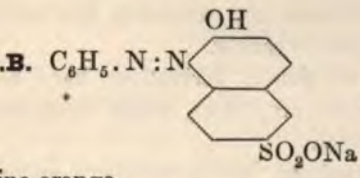
Trypan Red is a benzidine dye obtained from benzidine-monosulphonic acid by diazotization and combination with the sodium salt of the disulphonic acid of β-naphthylamine. It has the following constitutional formula:—

[1] For toxicity of dye-stuffs, see G. M. Meyer, *American Chem. Soc.*, vol. 29, p. 892, 1907.

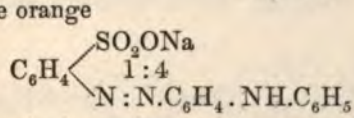


Ehrlich and Shiga experimented with this substance on mice infected with trypanosomiasis. 1 per cent. solutions were injected subcutaneously in doses of ·5 to 1·0 c.c. This had a very marked though temporary destructive action on the parasites, which the observers attributed to a special effect on the body of the host, leading to the production of parasiticidal substances. Animals after cure were protected to a great extent against a second infection.

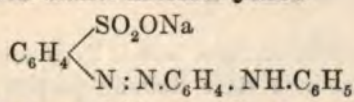
Trypan Blue (prepared by Nicolle and Mesnil), though differing in chemical constitution, has an action similar to that of trypan red on the trypanosomes; Ehrlich states that strains rendered resistant to the one are also immune to the other, though they may be destroyed by fuchsin or by the use of atoxyl (the sodium salt of *para* amido-phenyl-arsenic acid). Thus in Ehrlich's words [1] this specific resistance constitutes a *cribrum therapeuticum* or therapeutic sieve, by which any new remedy of this type may be classified. He possesses a strain of trypanosomes which are resistant to all these pharmacodynamic agents; and thus, if a mouse infected with this strain is cured by any new drug, the latter cannot belong to one of these classes.

Ponceau 4 G.B.  is non-toxic.

Di-phenylamine orange



produces albuminuria, but otherwise has only slight toxic action; on the other hand its isomer **Metanil yellow**



is toxic for dogs in doses of 20 gms. after 4 days. This is probably due to the presence of free diphenylamine.

[1] Harben Lecture, 1907, *Lancet*, ii, 1907, p. 351.

Class III.

Di- and Tri-phenyl-methane Dyes.

Among the diphenyl-methane dyes is **Pyoktanin,** in its pure state termed **Auramin O** (mixed with dextrin it goes by the name of Auramin I, II, III). It is the hydrochloride of imido-tetramethyl-diamido-diphenyl methane—

$$(CH_3)_2N.C_6H_4.C(=NH).C_6H_4N(CH_3)_2HCl$$

Brilliant Green, also known as malachite green G, and diamond green G, or ethyl green, is the sulphate of tetraethyl-di-*para*-amido-triphenyl-carbidride,

$$C_6H_5.C\begin{cases}C_6H_4N(C_2H_5)_2\\ C_6H_4:N(C_2H_5)_2\end{cases}.H_2SO_4.$$

It has already been mentioned, owing to the fact that it has been employed by Wendelstadt to destroy the trypanosomes of tse-tse fly disease.

Methyl Violet is a mixture of the hydrochlorides of the hexa-methyl-pararosaniline,

$$[(CH_3)_2N.C_6H_4]_2:C{=}C_6H_4{=}N\begin{cases}Cl\\ (CH_3)_2,\end{cases}$$

and penta-methyl-benzyl-pararosaniline; it is a stronger antiseptic than the yellow pyoktanin and relatively less toxic. It has been used locally for inoperable cancer.

A large number of similar derivatives have been studied and found to have antiseptic properties, which differ but slightly from those of the parent dyes.

Rosaniline or **Fuchsin** has a constitution expressed by the following formula—

$$\begin{matrix}NH_2.C_2H_4\\ NH_2\\ CH_3\end{matrix}\!\!>C_6H_3\!>C{=}C_6H_4{=}NH_2Cl$$

p-Fuchsin or *para*-**Magenta** (pararosaniline) does not contain a methyl group.

The antiseptic powers of these bodies have never been shown to be in direct relation with their staining properties, but appear to depend entirely on the presence of the aromatic nuclei.

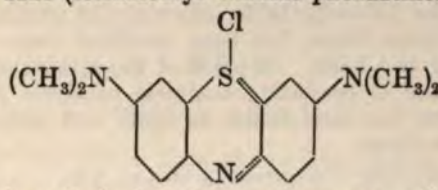
Eosin, the alkali salt of tetrabromfluorescein, has been shown by Noguchi to have the power of neutralizing certain toxins occurring

in cobra and other snake venoms. Although possessing no power of neutralizing the neurotoxins, it has marked action on the haemorrhagin and thrombokinase, which are important constituents of the venoms of the crotalus (rattlesnake) and daboia.

Class IV.

Thiazine Dyes.

Methylene blue (tetramethyl-diamido-phenazthionium chloride),

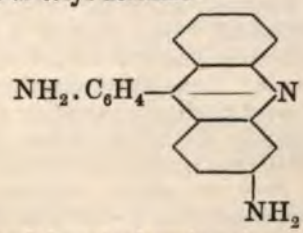


has been tried in malaria, but does not compare with quinine; its power of staining motor nerve endings suggested its use in neuralgia and rheumatic affections, but its action is uncertain. It has slight antipyretic and diuretic properties. In large doses it is a powerful irritant. Gautrelet and Bernard showed that in rabbits it caused a fall in urea excretion and some decrease in the secretory activity of the kidneys. Other aniline dyes acted similarly, namely, neutral red, fuchsin, methyl violet, gentian violet, and eosin. On the other hand, nigrosin (an indulin dye), and blue marine (water blue, china blue), a sulphonated triphenyl-rosaniline, did not produce this effect.

Class V.

Acridine Dyes.

Phosphine (Philadelphia yellow) is a mixture of the hydrochlorides of asymmetrical diamido-triphenyl-acridine with its homologue diamido-*m*-tolyl-acridine—



Phosphine is a powerful protoplasmic poison, especially for protozoa. It is a local irritant and moderately toxic. It has been tried as a substitute for quinine in malaria, but does not seem to have been successful. It is absorbed with difficulty from the stomach.

APPENDIX

PAGE 20. The following table, showing the curare-like action of various ammonium bases, has been modified from one given by H. Hildebrandt and Loos. In place of the minimum dose of each substance capable of producing complete paralysis per kilo. body-weight, curarine has been taken as unity and proportional values assigned to the others.

The minimum dose of curarine is ·008 m. gm.

	Curarine	1
1.	Methyl-strychnine sulphate	100
	Methyl ester of strychnine-iodoacetic acid	187
	Ethyl-strychnine sulphate	312
2.	Benzyl-atropine bromide	75
3.	Benzyl-brucine bromide	187
	Methyl-brucine iodide	312
4.	Methyl-cinchonine sulphate	312
	Methyl ester of cinchonine-iodoacetic acid	375
	Amyl-cinchonine iodide	625
5.	Tetra-methyl-ammonium iodide	625
6.	Benzyl-nicotine iodide	3750
	Methyl-nicotine sulphate	12500
	Ethyl-nicotine iodide	18750
7.	Benzyl-tropine iodide	7500
	Methyl ester of tropine-iodoacetic acid	12500

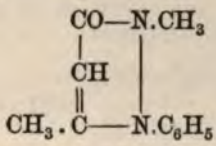
PAGE 54. There are a certain number of ammonium bases which do not produce a curare-like effect. Thus Fraser and Crum Brown showed that when the methyl and halogen groups were attached to the nitrogen in the pyrrolidine ring of nicotine there was no curare action; this appeared, however, when the nitrogen in the pyridine ring was made quinquevalent. Loos showed many years ago that the intensity of the curare-like action depended largely on the nature of the added alkyl groups. Thus ethyl strychnine sulphate, ethyl nicotine sulphate, and amyl cinchonine sulphate are respectively less active than the corresponding methyl-sulphates. The chlormethylate of papaverine (Pohl) and the corresponding derivatives of cotarnine and hydrastinine (Führer) have no action whatever. The variety of halogen makes no difference to the production of the curare effect, but considerable differences are noted if oxygen takes the place of the halogen element (Hildebrandt).

PAGE 64. Hildebrandt states that whereas *o*-oxybenzoic acid (salicylic acid) leaves the body conjugated with glycine, the *para*

compound is eliminated as a glycuronic acid derivative (Zeitschr. physiol. chem. 1904, Bd. xliii).

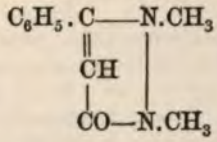
PAGE 207. Kobert has investigated various substances of the antipyrine type with the following results:—

3-Antipyrine according to Michaelis is constituted as follows—

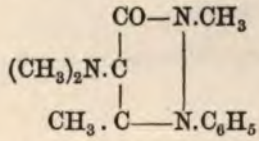


It is a more active poison than the ordinary 5-antipyrine; this is apparently directly traceable to the different way in which the carbonyl group is linked in the two substances.

On the other hand *iso*-antipyrine, formulated by Michaelis



is less toxic than 3-antipyrine, but more so than ordinary antipyrine; whereas pyramidon has a more powerful action than antipyrine, 3-pyramidon



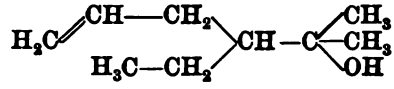
has a slighter action, and, further, is much less toxic than the parent substance, 3-antipyrine; that is to say, the entrance of the $N(CH_3)_2$ group into ordinary antipyrine increases the action, whereas a decrease follows its introduction into 3-antipyrine or into *iso*-antipyrine.

PAGE 272. Führer has recently shown that quinoline is oxidized in the body to *para*-oxy-quinoline, thus exactly resembling aniline.

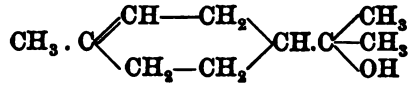
PAGE 288. Hydroberberine is the stereo-isomer of canadine, an alkaloid occurring in very small quantities in *Hydrastis canadensis*; corydaline, from *Corydalis cava*, is structurally very similar to the methyl substitution product of hydroberberine (F. Meyer), and is physiologically inactive. The corresponding ethyl derivative slows the respiration and pulse rate, but has no influence on the blood pressure (Meyer and Heinz).

PAGE 338. Further examples of the influence of stereo-chemical differences on taste are: (1) leucin, the *laevo*-rotatory variety of which is bitter, whilst the *dextro*-rotatory variety is sweet (E. Fischer and Warburg); (2) tryptophane, which when occurring in the body is almost tasteless, whereas the artificially prepared substance is sweet (Ellinger).

PAGE 346. Perkin has shown that closure of an aromatic ring does not necessarily produce any alteration in the odour of a substance. He instances the aliphatic terpineol—



and the corresponding cyclic body



PAGE 352. Ehrlich [1] has investigated various substituted rosanilines with regard to their action on trypanosomes.

There is a decreased activity in the di- and tri-oxy derivatives of malachite green and in *ortho*-oxy-hexamethyl-rosaniline; on the other hand, trimethoxy-pararosaniline is a more powerful trypanocide than the oxy derivatives of malachite green or methyl violet.

The introduction of carboxyl radicals has a much more marked effect in diminishing the action; thus chrome-violet, chrome-blue and azo-green are almost inactive.

[1] Berl. Klin. Wochenschr. Nos. 9-12, 1907.

INDEX

Abrastol, 139.
Acetal, physiological action of, 104.
Acetaldehyde, preparation of, 36.
Acetamide, 124.
Acetamide and oxamide, partial oxidation in body of, 74.
Acetanido-phenol-benzoate, 195.
Acetanilide, 181.
Acetic acid, determination of constitutional formula, 10; preparation of, 117; reactions with, in body, 66.
Acetoacetic acid, 113.
Acetone, 112, 113.
— -diethyl-sulphone, 114.
Acetoneamine derivatives, comparison with ecgonine, 306.
Acetophenone, 114.
Acetyl chloride, reactions of, 36.
Acetyl-codeine, 294.
Acetylene, chemical properties, 27; metallic derivatives of, 28; physiological action of, 45; preparation of, 33, 34.
— di-iod-, 50.
Acetyl-progallol, 147.
— radical, 120; introduction of, during pasage of substances through body, 6.
Acetyl-salicylic acid, 158.
Acid-amides, physiological properties of, 124 178; preparation and properties, 123.
Acid radicals, introduction of, into basic sustances, 120.
Acid, salicylic, dissociation of, 16.
Acidol, 17.
Acids, amido-, taste of, 335.
— aromatic, physiological action, 119, 120; syntheses with glycine in body, 63.
— halogen substitution products of aliphatic 121, 122.
— hydroxyaromatic, 149.
— physiological effect following replacemen of H in COOH group, 48.
— physiological properties of the, 118; preparation and properties of, 117, 118.
Acoine, 314.
Aconitic acid, 51.
Aconitine, 11.
Acrolein, 50.
Adrenalin, 317.
Adrenalone, 318.
— derivatives, 319.
Aesculin, 324.
Agathin, 202.
Agurin, 228.
Aitken, on smell, 332.
Alcaptonuria, 75.
Alcohols, aliphatic, classification, 87.
Alcohols and derivatives, 81; taste of, 334.
Alcohols, chemical characteristics, 90; comparison of physiological action of primary, 92; comparison of primary and secondary, 52; comparison of physiological action of primary, secondary, and tertiary, 92; effect on physiological action of replacement of hydrogen of OH group, 47; general methods of preparation, 88; general physiological properties, 91; general properties, 89; polyhydric, 90; secondary and tertiary preparation of, 89; used in perfumery, 344.
Aldehydes, action of sodium bi-sulphite on, 106.
— aromatic, physiological action, 107; halogen substitution products of aliphatic, 108; physiological action of, 107; polymerization of, 107; preparation of, 105; properties of, 104, 105; used in perfumery, 344.
Aliphatic alcohols, classification, 87.
Aliphatic and aromatic derivatives, subdivisions, 13.
Aliphatic and aromatic series, relative pharmacological action, 20.
Aliphatic derivatives, general methods of synthesis, 35; synthesis from acetic acid, 36; synthesis from alcohols, 36; synthesis from halogen derivatives, 37.
Aliphatic dibasic acids, taste of, 338.
Aliphatic hydrocarbons, 24; physiological characteristics, 45.
Alkali-iodides, organic substitutes, 167.
Alkaloids, 233; action of substituting groups, 245; alkyl substituents, action of, 245; bitter taste of, 340;

classification of, 244; curare action of quinquevalent nitrogen derivatives, **54**; general physiological characteristics, 243; Loew's special poisons, 249; opium, 288; opium, containing *iso*-quinoline ring, 299; pyridine group of, 249.
Alkyl and oxy-alkyl derivatives of uric acid, 225.
— ureas, preparation of, 215.
Allyl-alcohol, 50.
— sulphide, 127.
— thiourea, 218.
— trimethyl ammonium hydrate, 51.
Allylamine, 50.
Aloin, 329.
Alypin, 314.
Amido-acetamide, 124.
Amido-acetic acid, derivatives of, formed in body, **63**.
— (glycine), formation of derivatives in body with:— benzoic acid, 63; *p*-brom-benzene, 63; chlorbenzoic acid, 63; cuminic acids, 63; mesitylenic acid, 63; naphthoic acids, 63; nitrobenzoic acid, 63; *p*-nitro-toluene, 63; phenyl acetic acid, 64; salicylic acid, 63; xylene, 63.
— syntheses with, in body, 56.
Amido-acids, aliphatic, taste of, 335; aromatic, taste of, 336; oxidation of, in body, 74; γ taste of, 340.
Amido-benzoic acid, formation of urea derivative in body, 64.
α-Amido-cinnamic acid, oxidation of, in body, 75.
Amido-dibasic acids, taste of, 338.
p-Amido-phenol, derivatives of, 184; types of derivatives, 186.
Amido-salicylic acid, formation of urea derivative in body, 64.
Amido-valerianic acid, taste of, 335.
Amines, action of nitrous acid on, 89.
— aliphatic, physiological action of, 47.
— aromatic, preparation of, 173, 174.
— classification, 171; effect produced by entrance of acidic groups, 176, 177; general methods of preparation, 172; physiological properties of, 177; preparation of, 37, 38; primary, 171; primary, secondary, and tertiary reactions of, 175; properties of, 175; tertiary, 171.
Aminoform, 108.
Ammonia, derivatives of, 171; summary of physiological action of, 207.
— physiological properties of, 177.
Ammonium bases, curareform action, **14**, 20.
Ammonium compounds, quaternary, physiological action of, 179.
Amygdalin, 324.
Amygdophenin, 191.
Amyl-acetate, 122.
— alcohol, derivatives with local anaesthetic action, 314.
— nitrite, 100.
— radical, influence on odour, 342
Amylene hydrate, 93.
Anaesthesin, 312.
Anaesthetic action of benzoic acid derivatives, 310.
— power of glycocoll derivatives of benzoic acids, 311.
Anaesthetics and hypnotics, distinction between, 81; main group of, 81.
Anesin, 96.
Aneson, 96, 315.
Anilides, physiological actionof, 179; preparation of, 176; stablity of, 176.
Aniline and phenol derivatives, comparison of physiological ation of, 210.
— and thiophene, increased toxicity on introduction of alkyls, 46.
— methyl and ethyl, physiological properties of, 178.
Aniline, derivatives, 181.
— — physiological action of, 81.
— — primary and secondar derivatives, 47.
Anilopyrine, 206.
Anisanilide, 182.
Anisol, 129.
Annidalin, 163.
Anthracene, 30.
Anthraquinone derivatives, 29; purgatives, 328.
Antifebrin, 181.
Antiosin, 167.
Antipyretics, main group ofynthetic, 171.
Antipyrine, 48, **204**.
— chloral, 111.
— physiological action of, 204, 205, 209.
— preparation of, 202.
— salicylic acid salts of, 2[illegible].
Antiseptics, aromatic, 128
— containing iodine, 161; omparison of, 167.
Antispasmin, 301.
Antithermin, 201.
Anytin, 169.
Anytols, 169.
Apocodeine, 301, **302**.
Apolysin, 192.
Apomorphine, 301.
Arabino-chloralose, 111.

Arbutin, 323.
Aristol, 163.
Aristoquin, 279, 280.
Aromatic acids, physiological action of, 119, 120.
— antiseptics, 128.
— derivatives, action of nitric and sulphuric acid on, 40; outline of synthetic methods for preparation of, 40; oxidation of in organism, 75.
— esters of halogen acids, 99.
— halogen derivatives, preparation from diazo-compounds, 40; stability of, 99.
— hydrocarbons, preparation from diazo-derivatives, 40.
— hydroxy acids, 149.
— hydroxyl derivatives, 128.
— ketones, preparation of, 42.
— nitro derivatives, 101.
— substances oxidized in body :—aniline, 78; benzene, 76; benzidine, 78; cymene, 76; di-phenyl, 78; ethyl-benzene, 76; indol, 78; naphthalene, 76; nitro-toluene, 77; phenyl-methane, 78; phenyl-propionic acid, 77; propyl-benzene, 76; toluene, 76.
— substances, physiological action following introduction of COOH group, 119.
Arsonium bases, physiological action, 54.
Asaprol, 139.
Asparagine, *dextro*, and *laevo*, difference in taste, 53.
Aspirin, 158.
Asymmetric carbon atom, theory of, 5.
Atropine, 264; central actions of, 267; comparison with cocaine, 266; constitution of, 265; effect on eye compared with cocaine, 270; mydriatic action, 270; paralysis of nerve endings to involuntary muscle, 267; paralysis of sensory nerve endings caused by, 271; physiological action dependent on two optical isomers, 271; physiological action of, 265; substitutes, 316.
Auramin O, 354.
Aurantia, 351.
Auxochrome groups of Witt, 348.
Avogadro's hypothesis, 1.
Azo-dyes, 351.
— physiological action of, 352.

Bactericidal action of dyes, 349.
Baglioni, theory of narcosis, 86.
Bauman and Kast on sulphonals, 114, 115.
Bechhold and Ehrlich, antiseptic value of phenols, 134.
Benzaldehyde, preparation of, 105.
Benzamide, 124.
Benzanilide, 182.
Benzene, determination of constitutional formula, 11, 12.
Benzene-derivatives, comparison of toxicity of isomers, 52; different types of, 43.
Benzene homologues, oxidation of, 30; reduction of, 31; physiological action, 46; preparation of, 33; synthesis of, 42.
Benzene hydrocarbons, 28; nature of double bonds in, 28, 29.
Benzene nucleus, negative characteristics of, 29.
Benzene, physiological action of, 45; sources of, 30; stability of ring complex, 30.
Benzene sulphonic acids, preparation of, 41.
Benzenes, di-oxy, taste of, 339.
Benzidine, not oxidized in body, 78; value in dye industry, 351.
Benzoic acid, **149**; derivatives, with local anaesthetic action, 310.
Benzo-naphthol, 139.
Benzonitrile, 126.
Benzophenone, 114.
Benzosal, 144.
Benzosalin, 158.
Benzoyl-arbutin, 323.
Benzoyl-lupinene, 180.
Benzoyl-morphine, 296.
Benzoyl radical, 120.
Benzoyl-salicin, taste of, 335.
Benzylamine, 173.
Benzyl chloride and chlortoluene, comparison, 43.
Berberine, 287.
Betaine, 178.
Betol, 139.
Bile, action of, 55.
Bismark brown, 352.
Bisulphide of carbon, 127.
Bokorny, comparison of toxicity of benzene isomers, 52.
Borneol, glycuronic acid derivatives of, 62.
Bredig on colloidal solutions, 86.
Brilliant green, 354.
Brom-acetic acid, 122.
Bromal, 109.
Bromalin, 98.
Brom-benzene, 99.
Bromine, derivatives of urea, 217.
Bromine, organic preparations of, for epilepsy, 98.
Bromipin, 98.
Bromoform, 98.
Bromural, 217.
Brucine, 281.

Brunton and Cash, ammonium compounds, 20.
Butyl-amide, 124.
Butyl-chloral, 109.
— reduction of, in body, 79.
iso-Butyl-o-cresol, 163.
Butyric acid, 119.
Butyronitrile, 126.

Caffeine, 227.
Caffeine, effect of introduction of (OH) group, 92.
Cahn and Hepp, aniline derivatives, 181.
Camphor, glycuronic acid derivatives of, 62.
Carbamic esters of guaiacol, 143.
Carbon-bisulphide, 127.
Carbon, tendency to self-combination, 7.
Carbon tetrachloride, 97.
Carbonic acid, ammonia derivatives of, 213.
Carbostyril, synthesis with glycuronic acid, 61.
Carvacrol, 130.
Cash and Dunstan, on nitrous esters, 100.
Catalytic poisons, 17.
Catechol, causing rise of arterial pressure, 318.
Cellotropin, 323.
Cells, selective action of, 19; staining reactions, 19.
Cevine, decomposition product of veratrine, 180.
Chain into cyclic derivatives, effect on taste, 340.
'Chemical Environment,' Ehrlich's views, 349.
Chloracetic acids, physiological properties of, 121.
Chloral, 108, 109.
Chloral-acetophenone, 110.
Chloral-alcoholate, 110.
Chloral-amide, 110.
Chloral-ammonia, 111.
Chloral-antipyrine, 111.
Chloral-formamide, 110.
Chloral, formation of urochloralic acid in body, 60; reduction of, in body, 79.
Chloral-hydrate, 106.
— production of surgical anaesthesia, 81.
Chloral-urethane, 110.
Chloralose, 111.
Chlorbenzene, 99.
Chlor-caffeine, physiological action of, 95.
Chloretone, 96, 315.
Chlorides of carbon, physiological action of, 95.
Chlorinated phenols, antiseptic action of, 134.
Chlorine, physiological characteristics following entrance of, 95.
Chloroform, 96, 97.
Chloroform acetone, 315.
Chloroform, 'delayed poisoning,' 97; fall of temperature after narcotic doses, 16.
Chlor-toluene and benzylchloride, comparison, 43.
Choline, 51.
Chromium oxychloride, preparation of aromatic aldehyde, 105.
Chrysin, 328.
Chrysoidin, 352.
Chrysophanic acid, 328.
Cinchona alkaloids, 271.
Cinchonine, oxidation of in organism, 277.
Cinchonine and quinine, 276.
Cinchotoxine, 277.
Cinnamic acid, 51, 149; oxidation in body, 77.
Citral, 344.
Citric acid derivatives of phenetidin, 192.
Citronellol, 344.
Citrophen, 192.
Coca-ethyline, 262.
Coca-propyline, 262.
Cocaine, 120, 180, **258.**
a-Cocaine, 263.
Cocaine, action of (CH_3COO) group, 262; action of (C_6H_4COO) group, 263; 'anaesthiophore' group, 264; classification of physiological action, 258; comparison with atropine, 266; derivatives, 261; *dextro*, *laevo*, difference in action of, 53; elevation of temperature effect, 260; mydriatic action of, 260; production of local anaesthesia, 260; relations between physiological action and constitution, 264; substitutes for, 304.
Cocaine-urethane, 262.
Codeine, 294.
— acetyl derivative of, 294; chloride of, 296.
Colloidal solutions, 86.
Compound radicals, theory of, 1.
Conhydrine, 252.
Coniceines, 252.
Coniferin, 324.
Coniine, 252.
iso-Coniine, 252.
Coniine derivatives, 252.
Coniine, synthesis of, 236.
Constitutional formulae, factors required, 9; acetic acid, 10; benzene, 11.
Copellidine, 254.

Cosparin, 182.
Cotarnine, 285, **286**, 300.
Cotoin, 325.
Coumarin, 346.
Creolin, 133.
Creosotal, 142.
Creosote, 141.
— derivatives, general remarks on, **146.**
— esters of, 141.
Cresol, tri-iodo, 166.
Cresols, 130, **132.**
— action on nitrogenous equilibrium, 133, 134.
Cresotinic acids, 151.
Crum Brown and Fraser, ammonium compounds, 20.
Crystallose, 337.
Cupreine, 276.
Curare-like action of ammonium bases, 20, 179; of arsenic, antimony, and phosphorus bases, 179; of quinoline derivatives, 272.
Cushny, benzene derivatives with high distribution coefficient, 85.
Cushny, hyoscyamine, 271.
Cyanogen, 126.
Cyclic ketones, 246, **248.**
Cyclic ureides, 219.
Cyclo-paraffins, preparation of, 33.
Cyllin, 133.
Cymene, oxidation of in body, 76.
Cystamine, 108.
Cystin derivatives, formation of in body, 66.
Cystogen, 108.

Decahydro-quinoline, 272.
Desichthyol, 169.
Desoxy-caffeine, 227.
Desoxy-quinine, 278.
Desoxy-strychnine, 282.
Desoxy-theobromine, 227.
Diabetes, formation of acids in, 77.
Di-acetone-amine, 304.
Di-azo derivatives, preparation and reactions, 40, 41.
Dichlorethane, 97.
Diethylamine, preparation of, 173.
Diethyl-ketone, 113.
Diethyl-malonyl-urea, 219.
Diffusion velocity in relation to physiological reactivity, 16.
Digitonin, 330.
Dihydrostrychnoline, 282.
p-Dihydroxy-diphenyl, 135.
Dimethyl-benzamide, 124.
Dimethyl-ethyl-acetic acid, 119.
Dimethyl-sulphide, physiological action on passage to tetravalent derivatives, 54.
Dinitro-cresol, 350.
Dionine, 294.
Dioxybenzenes, physiological action of, 132, 140.
Diphenyl-dihydro-quinazoline, 241.
Diphenyl derivatives, antiseptic value of, 135.
Diphenyl-methane dyes, 354.
Diphenyl, oxidation in body, 78; physiological action of, 45.
Dipropyl-ketone, 113.
Dissociation and physiological action, 15, 16.
Distribution, coefficient, 83, 84.
— coefficient and liminal values, comparison of, 84.
— coefficient of sulphonals, 84.
— of dye-stuffs, influence of other substances on, 349.
— of poisons and drugs in body, 349.
Di-thymol-di-iodide, 163.
Diuretin, 228.
Dormiol, 110.
Dosage, effect of, 16.
Drug, 'anchoring' group, 21.
—, its main action and bye-effects, 16.
Drugs, selective action of, 18, 23.
Dujardin-Beaumetz, influence of substituents in aromatic series, 21.
Dulcin, 340.
Dunstan and Cash on nitrous esters, 100.
Duotal, 142.
Dyes, 347.
— azo series of, 351.
— bactericidal action of, 349.
— di- and tri-phenyl methane series of, 354.
— nitro derivatives of paraffins, 350.
— theory of, 22, 348.
— thiazine group of, 355.

Ecgonine, 259.
— anhydride of, 262.
— benzoyl derivative, 259.
— complex, theory of physiological action of, 260.
— methyl ester, 180, 259.
— phenyl-acetyl ester of, 264.
Ehrlich, criticism of Loew's theory, 348; observations on dyeing properties of substances containing C_2H_5 groups, 49; physiological action compared with theory of dyes, 21; side-chain theory, 19.
Ehrlich and Bechholdt, antiseptic value of phenols, 134.
Einhorn and Heintz, on esters of oxy-amido-benzoic acids, 310.
Emodine, 328.
Empirical formulae, 9, 10.
Enzymes, 53.

Eosin, 354.
Eosote, 144.
Epicarin, 140.
Epiosin, 293.
Erythrol tetranitrate, 101.
Esters, general methods of preparation, 90, 94, 122; general properties, 94; physiological properties, 122, 123.
— of halogen acids, 93.
— of hydriodic acid, 99.
— of hydrobromic acid, 98.
— of hydrochloric acid, 96.
— of inorganic acids, 93–103.
— of nitrous and nitric acids, 100.
— of salicylic acid, odour of, 342.
— of sulphurous and sulphuric acids, 102.
— used in perfumery, 344.
Ethers, formation from alcohols resulting in lessened toxicity, 47; physiological action of, 103; preparation and properties of, 103, 104.
Ethoxy-caffeine, 229.
p-Ethoxy-phenyl-succinimide, 190.
Ethyl acetate, 122, 123.
Ethyl alcohol, preparation of, 88.
Ethylamine, decomposition by nitrous acid, 89.
Ethyl-benzamide, 124.
Ethyl bromide, 98.
Ethyl chloride, 96.
Ethyl ester of tyrosin, 123.
Ethyl-formate, 122.
Ethyl-guaiacol carbonate, 142.
Ethyl iodide, 99.
Ethyl mercaptan, 114.
Ethyl and methyl groups, physiological differences, 49.
Ethyl-salicylate, 153.
Ethylene, physiological action of, 45.
Ethylene dibromide, 98.
Ethylene-diethyl-sulphone, 115.
Ethylene-dimorphine, 293.
Ethylene hydrocarbons, preparation of, 33, 34.
Ethylidene-dimethyl-sulphone, 115.
Eucaine, A and B (*α* and *β*), 307.
Eudoxin, 167.
Eugallol, 147.
Eugenol, 131.
— use in perfumery, 345.
Eumydrine, 317.
Euphorin, 183, 196, 213.
Euphthalmine, 316.
Euporphin, 302.
Eupyrin, 195.
Euquinine, 279.
Euresol, 141.
Europhen, 163.
Exalgin, 184, 210.
Exodine, 330.

Ferrichthyol, 169.
Fischer and Filehne on Kairine, 49.
Fisetin, 327.
Formaldehyde, 71.
— compounds of, 107, 108.
Formalin, 71.
Formamide, 124.
Formamint, 107.
Formanilide, 182.
Formic acid, antiseptic properties, 118.
Formin, 108.
Formyl-phenetidin, 189.
Formyl-urea, 108.
Fortoin, 326.
Fraser and Crum Brown, ammonium compounds, 20.
Freundlich and Losev, Theory of dyeing, 22.
Friedel and Craft's synthesis, 42.
Fuchsin, 354.
Fumaric acid, 119.
Furfurane, physiological action of, 45.
Furfurol, synthesis with acetic acid in body, 66.

Gallacetophenone, 58, 148.
Gallic acid, 132, 159.
Gaultherin, 322.
Gentisinic acid, 57.
Geosote, 144.
Geraniol, 344.
Glucosides, 320.
— classification, 320; taste of, 333, 334.
Glutaminic acid, *dextro* and *laevo*, difference in taste, 53.
Glutaric acid, 119.
Glycine, derivatives of, formed in body, 63.
Glycocoll, derivatives of amido and oxy-amido benzoic acids, 311.
— derivatives of, formed in body, 63.
Glycocoll-phenetidin, 193.
Glycol, preparation of, 88.
Glycosal, 154.
Glycuronic acid derivatives, **59**.
Glycuronic acid, derivatives of, formed in body :—borneol, 62; camphor, 62; choral, 60; dichloracetone, 61; menthol, 62; naphthol, 62; pinacone, 61; pinene, 62; phellandrene, 62; phenetol, 62; primary alcohols, 61; sabinene, 62; thujon, 62; vanillin, 61.
— — substances causing appearance of in urine, 59; substances which form derivatives with, 61; syntheses with, in body, 56.
Griserin, 165.
Guaiacetin, 146.
Guaiacol, 142.
— attempts to increase solubility of,

145; carbamic esters of, 143; inorganic esters of, 142, 143; oleate, 143; organic esters of, 143; sulphonates of, 145.
Guaiacolsalol, 144.
Guaiacophosphal, 143.
Guaiamar, 146.
Guaiasanol, 145.
Guanidine, 178.

Halogen acids, aromatic esters of, 99.
Halogen derivatives of aromatic series, stability of, 173.
Halogens, influence on odour, 342.
Hedonal, 82, **214**.
Helicin, 322.
Heptane, 25.
Heroine, 180, **295**.
Hesperidin, 325.
Heteroxanthine, 226.
Hetocresol, 150.
Hetol, 149.
Hexamethylene-tetramine, 108.
— and iodoform, 162.
— tannic acid, derivatives of, 160.
Hexane, 25, 45.
Hinsberg and Trenpel on aniline derivatives, 185.
Hippuric acid, formation of in body, 63.
Holocaine, 313.
Homatropine, 264, 268.
Homogentisinic acid, 57.
Homologous derivatives, smell of, 342.
Honthin, 160.
Hordenine, 303.
Hydracetin, 200.
Hydrastine, 284.
Hydrastinine, 285, **286**.
Hydrastininic acid, 286.
Hydriodic acid, esters of, 99.
Hydrobromic acid, esters of, 98.
Hydrocarbons, aliphatic, 24.
Hydrocarbons, aliphatic aromatic taste of, 335; aliphatic not oxidized in the body, 71; benzene, 28; benzene, sources of, 30; methods of preparation, 32; paraffins, 24; paraffins, preparation of, 32; physiological characteristics, 45.
Hydrochloric acid, esters of, 98.
Hydrocotarnine, 286.
Hydroquinine, 278.
Hydroquinone, 57, 131, 140.
— taste of, 339.
Hydroxy acids, aromatic, 149.
Hydroxy-benzoic acids, 119, 120.
Hydroxy-propane, iodine derivatives, 168.
Hydroxyl derivatives, aromatic, 128.
Hydroxylamine, action on aldehyde, 106.
Hyoscyamine, 270.
Hypnal, 111, 206.
Hypnone, 114.
Hypnosis, theory of Overton and Meyer, 83, 84; views on, 85, 86.
Hypnotic action of ureides, 219, 220.
Hypnotics and anaesthetics, distinction between, 81; main group of, 81.

Ichthalbin, 169.
Ichthargan, 169.
Ichthoform, 169.
Ichthyol, 169.
— efficacy dependent on several factors, 170.
Imido acids, taste of, 338.
Imido-derivatives, effect of replacing H of NH group by alkyls, 48.
Indican, urine, 79.
Indol, oxidation in body, 78.
Indophenol reaction, with aniline derivatives, 185.
Inertia of carbon systems, 8.
Intestines, action of alkali in, 55.
Iodal, 109.
Iodalbin, 167.
Iodeigon, 162.
Iodide of *iso*-butyl-o-cresol, 163.
Iodides, organic substitutes, 167.
Iodine antiseptics, comparison of, 167.
Iodine, containing antiseptics, 161; entrance into aliphatic and aromatic substances, 163.
Iodipin, 167.
Iodo-anisol, 166.
Iodo-compounds, aromatic, 99.
Iodoform, 99, 161, 162.
Iodoform, classes of substitutes, 161, 162.
Iodoformal, 162.
Iodoformin, 162.
Iodoformogen, 162.
Iodol, 164.
Iodolene, 162.
Iodyloform, 162.
Ionone, 345.
Iothion, 168.
Iridin, 326.
Irigenin, 326.
Isomeric relationships, influence on sense of smell, 345.
Isomerism, 4, 5.
— interdependence of physiological action, 51.
Iso-oximes, cyclic ketones, 246, **248**.
Iso-pilocarpine, 232.
Isopral, 95.
iso-quinoline, constitution of, 240.

Jaborine, 232.
Jalapin, 322.

Kairine, 49, 275.
Kairolin A, B, 274.
Kaiser yellow, 351.
Ketones, aromatic, oxidation of, in body, 57; preparation of, 42; classification and preparation, 112; cylic, 246, **248**; preparation of, 36, 37; properties of, 112; reaction with phenyl-hydrazine, &c., 112; used in perfumery, 345.
Ketonic acids, stability of, 113.
Kobert's paradox, 19.

Lactamide, 124.
Lactic acid, appearance in urine, 73.
Lactophenin, 189.
Lactylamido-phenol-ethyl-carbonate, 195.
Lactyl-phenetidin, 189.
Lactyl radical, 120.
Lactyl-tropeine, 267.
Ladenburg's generalization on mydriatic action, 268.
Laudanine, 300.
Laudanosine, 299.
Lenigallol, 147.
Lepidine, 273.
'Leuco' compounds, 347.
Levulinic acid, 113.
Liminal values, 83, 84.
Linalool, 344.
Lipoid substances, solubility of narcotics in, 83.
Loew's 'substitution' theory, criticism by Ehrlich, 348; theory of poisons, 17.
Loretin, 164.
Losophane, 166.
Lupetidines, 253, 254.
Lupinene, 180.
Lysol, 133.
Lysol, sulphur preparation, 169.

Magnesium, organic derivatives, 38; synthesis with, 38.
Malachite green, 354; action on bacteria, 350.
Malakin, 194.
Malarin, 194.
Maleic acid, 119.
Malonic acid, 119.
Mannitol hexanitrate, 101.
Marsh gas, physiological action of, 45.
Martius's yellow, 350.
Mercaptans, **126**.
Mercapturic acids, formation of, in body, 67.
Mercury, bromide, chloride, cyanide, 15.
Mercury salts, double compounds of, 15, 16.
Merling, physiological action of acetone-amine derivatives, 306.
Mesotan, 154.
Metabolic changes of sulphonals, 116.
Metabolic processes, 55.
Metakalin, 133.
Metanicotine, 256.
Metanil yellow, 353.
Methacetin, 185.
Methane, preparation of, 32.
Metho-codeine, 297.
Methylacetate, 123.
Methyl alcohol, preparation of, 88.
Methyl and ethyl groups, physiological differences, 49.
Methyl-benzamide, 124.
Methylbromide, 98.
Methyl-chloroform, 97.
Methyl-coniine, 252.
Methylecgonine, 120.
Methyl-ethyl-ether, probable value of, 104.
Methyleuphorin, 184.
Methyl group, introduction of, during passage of substances through body, 66.
Methyl-keto trioxybenzene, 148.
Methyl nitrile, 125, 126.
Methyl rhodin, 158.
Methyl salicylate, 153.
Methyl sulphide, 127.
Methyl violet, 354.
Methylal, physiological action of, 104.
Methylene blue, 355.
Methylene diethyl-sulphone, 115.
Metramine, 108.
Mikrocidine, 139.
Molecular magnitude, determination of, 9.
Moore and Roaf, hypothesis on action of anaesthetic substances, 85; on chloroform, 85.
Morphenol, 291.
Morphigenin, 292.
Morphine, 290.
— benzoyl derivative, 296; constitution of, 291; derivatives of, 293; di-acetyl derivative, 295; ethyl derivative, 294; 'pyridine,' formula for, 302.
iso-Morphine, 297.
Morphol, 291.
Morpholine and phenanthrene, 242.
Morpholine-phenanthrene alkaloids, 288.
Morpho-quinoline ether, 296.
Morphothebaine, 299.
Musk, artificial, 345.
Mydriasine, 317.
Mydriatic action, Ladenburg's generalization, 268.

Naphthalan-morpholine, 291.
Naphthalene, 30.
— oxidation of, in body, 76; physiological action of, 45.
Naphthol, α- and β-, glycuronic acid derivatives of, 62.
Naphthol-sulphonic acid, 139.
Naphthols, **139.**
Naphthylamine-sulphonic acid, 140.
Narceine, 301.
Narcotic action, enhanced by entrance of chlorine into molecule, 82.
— of alcohols, aldehydes, ketones, 82.
Narcotic effects, depressed by carboxyl group, 82.
Narcotic properties of sulphones, 115, 116.
Narcotics, aliphatic, groups of, 82; physiological action of, 81.
Narcotine, 286, 300.
Narcyl, 301.
Nencki, salol principle, 55, 129; sulphocyanic acid in stomach, 65.
Neurine, 51.
Neurodin, 196.
Nicoteine, 256.
Nicotine, 255.
Nicotine, difference between *dextro* and *laevo*, 53.
Nirvanine, 311.
Nitriles, aromatic, 126.
— aromatic, preparation of, 41, 42.
— formation of sulphocyanides in body, 65.
— of fatty series, toxicity of, 126.
— odour of, 343; physiological properties, 125, 126; preparation of, 37, **125**; reactions of, 37, **125.**
iso-Nitriles, odour of, 343.
Nitrites, chemical action on tissue cells, 101.
Nitrobenzaldehyde, oxidation in body, 63.
m-Nitrobenzaldehyde, changes of, in body, 65.
Nitrobenzene, reduction of, in body, 79.
Nitro-compounds, aromatic, reduction of, 173.
Nitro-derivatives, aromatic series, physiological action, 101, 102.
— odour of, 342.
Nitro-glycerine, 101, 102.
Nitro-group, influence on taste, 334.
Nitro-naphthol, physiological action of, 102.
Nitro-paraffins, 101.
Nitro-phenol, 129.
Nitro-phenols, reduction of, by organism, 80.
Nitro-phenyl-propiolic acid, reduction of, by organism, 80.
Nitro-thiophene, physiological action of, 102.
Nitro-toluene, oxidation in body, 77.
Nitrogen, influence on odour, 343.
Nitrous and nitric acid, esters of, 100; physiological action of, 100.
Nölting, on oxidation processes in body, 78.
Nosophen, 166.
Novocain, 312.
Nux vomica, 271.

Octane, 25.
— physiological action of, 45.
Odour, 341.
— dependence on physical factors, 341.
Oil of Wintergreen, 153.
Olefines, chemical properties of, 26.
Opianic acid, physiological properties of, 286.
Opium alkaloids, 288; classification, 289; containing *iso*-quinoline ring, 299.
Optical isomers, 5.
Optically active tartaric acids, 6.
Orcin, 131.
Orcinol, taste of, 339.
Orexine, 241.
Organic dyes, 347.
Orthin, 201.
Orthoform, 310.
Orthoform-neu, 311.
'Osmophore' groups, 341, **342**; presence of several in molecule, 342.
Overton, Meyer and, theory of hypnosis, 83, 84.
Oxalic acid, oxidation in body of, 73; toxicity of, 118.
Oxalic and succinic acids, synthesis from ethylene, 39.
Oxidation, differences between methyl and ethyl groups, 71; general process of, 67, 68, 69.
— in organism, theories of, 70.
— of aromatic derivatives in body, 75.
— of aromatic substances, Nölting's rule, 78.
— of stereochemical isomerides, 69.
— processes in the body taking place with:—Alanin, 74; alcohols, 71; aliphatic acids, 73; aliphatic substances, 71; amido-acids, 74; dextrose, 69; esters, 71; formaldehyde, 71; formate of soda, 69; glutaric acid, 74; glycerol, 72; glycolic acid, 73; hydrocarbons, 71; malic acid, 74; malonic acid, 73; mannite, 69, 72; methyl alcohol, 71; methylamine, 71; nitriles, 71; oxalic acid, 73; oxy-acids, 73; oxy-butyric acid, 73;

phenylalanine, 69; secondary alcohols, 71; succinic acid, 73; sugars, 69, 72; tartaric acid, 69, 70, 73; tartronic acid, 73; tertiary alcohols, 71.
Oxidation, selective, 69, 70.
Oxidizing poisons, 17.
Oxy-benzenes, comparison of toxicity, 52; preparation and properties, 128.
Oxybenzoic acids, 150.
Oxybutyric acid, 118.
Oxycarbanil, 181.
Oxyphenacetin-salicylate, 195.

Paeonol, 58.
Pancreatic juice, action of, 55.
Papaverine, 299.
Parabino-chloralose, 111.
Paraffin hydrocarbons, 24; preparation of, 32.
Paraffins, chemical properties, 26; isomerism in the, 25; nitro-compounds of, 101; occurrence in nature, 25; physical properties of, 24.
Paraldehyde, 108.
Pararosaniline, 347.
Paraxanthine, 226.
Pasteur, chemical configuration and ferments, 53.
Penicillium glaucum, action on lactic acid, 7; on mandelic acid, 7.
Pentamethylene-diamine, 247.
Pentane, 25.
Pepper, glucosides of, 321.
Peptoiodeigon, 162.
Peronine, 296.
Petroleum emulsion, 45.
Petrosulphol, 169.
Pharmacology, relation to therapeutics, 14.
Phenacetin, 186, 187, **188**.
Phenacetin, attempts to increase solubility of, 191; theory of physiological action, 211.
Phenanthrene and morpholine, 242.
Phenetidin, derivatives, 189, 190; derivatives with local anaesthetic action, 313, 314; *ortho* and *meta* derivatives, 212.
Phenetol, 129.
— comparison with aliphatic ethers, 104; formation of chinaethonic acid from, in body, 62.
Phenocoll, 193.
Phenol and aniline derivatives, comparison of physiological action of, 210.
Phenol and phenol-ethers used in perfumery, 345.
Phenol, changes of, in body, 57; derivatives with local anaesthetic action, 313.
Phenol esters, 129.
Phenolphthalein, tetra-iodo, 166.
Phenols and phenol ethers, characteristic odour of, 343.
Phenols, antiseptic values, and general conclusions, 139; elimination of acidic nature of, 129, 130; homologous, 130; introduction of COOH group into, 150; local anaesthetic action of, 315; physiological action of, 131, 132; polyhydric, 130; preparation of, 128; preparation from diazo-compounds, 41; properties of, 129.
Phenol-sulphonic acid, 57.
Phenosal, 193.
Phenylacetamide, 124.
Phenyl acetate, 129.
Phenyl-acetic acid, antiseptic properties of, 118.
— synthesis with glycine in body, 64; with α-methyl-pyridine, 64.
Phenylacetylene and its derivatives, odour of, 343.
Phenylalanin, oxidation of, in body, 75.
Phenyl-azoimide, 208.
Phenyl-ethyl-ketone, 114.
Phenyl-ethylene, glucosides derived from, 324.
— (styrol), preparation of, 34.
Phenylhydrazine, action on aldehydes, 106; action on ketones, 113; derivatives of, 200, 201, 202; physiological action of, 199; preparation of, 41, 198; reactions of, 199.
Phenyl-methane, 183.
— derivatives, **196**.
Phenyl-propionic acid, oxidation of, in body, 64.
Phenyl radical, effect on taste, 334.
Phesin, 191.
Philadelphia yellow, 355.
Phloretin, 325.
Phlorizin, 325.
Phloroglucin, physiological action of, 132; taste of, 339.
Phosphate and phosphite of guaiacol, 143.
Phosphatol, 143.
Phosphine, 355.
Phosphonium bases, physiological action, 54.
Phosphotal, 143.
Phthalic acid, oxidation of, in body, 76; preparation of, 117.
Phthalide and its derivatives, odour of, 343.
Phthalimide, in preparation of am-

ines, 172; oxidation in the body, 76.
Picric acid, 129, 350.
Picryl chloride, 173.
Pilocarpidine, 232.
Pilocarpine, 231, 232.
— constitution of, 224.
Pinacol, 131.
Pinacones, physiological action of, 93.
Pipecolylalkin, 254.
Piperidine, physiological action of, 46, **250.**
Piperidon, 245.
— derivatives, 246.
Piperine, 255.
Piperonal, use in perfumery, 344.
Piperylalkin, 254.
Poisons, 'catalytic,' 17; Loew's theory, 17, 348; 'oxidizing,' 17; special, 18; 'substituting,' 17, 348.
Polygallic acid, 330.
Polyhydric phenols, 130.
Polymerization of aldehydes, 107.
Ponceau, 4 G. B., 353.
Populin, 323.
Populin, taste of, 335.
Primary amines, 171.
Propion, 113.
Propionamide, 124.
Propionitrile, 126.
Propyl-phenetidin, 189.
Propyl, *n*- and *iso*-, physiological action of, 92.
Protein, occurrence of tyrosin and phenylalanin in, 75.
Proteins, difficulty in determination of composition, 7.
Protocatechuic acid, 58.
Protoplasm, Loew's theory, 17.
Prussic acid, 125.
Pseudo-tropine, 270.
— benzoyl ester, 263.
Psoriasis, 148.
Purgatin, 329.
Purgatol, 329.
Purgen, 330.
Purification of organic compounds, 8; methods used, 8.
Purine derivatives, general review of, 229.
— group, 221.
— nomenclature, 221.
Purine, physiological action of, 224; synthesis of, 222.
Pyoktanin, 354.
Pyramidon, 206.
Pyrantin, 190.
Pyrazolon derivatives, 202.
Pyridine, action of oxidizing agents on, 235; action of reducing agents on, 236; and piperidine, 233; changes of, during passage through body, 66; comparison with quinoline, &c., 272; derivatives, differences in physiological action, 257; group of alkaloids, 249; homologues, physiological action, 46, 251, 253; physiological action of, 45, **250**; synthesis of, 234.
Pyrocatechol, 130, 140.
Pyrogallic acid, 131, 140, 147; taste of, 339.
Pyrrol and pyrrolidine, constitution of, 237.
— physiological action of, 45.
— tetra-iodo-, 164.
Pyrrolidine alkaloids, 258.
Pyrrolidon, **248.**

Quaternary ammonium compounds, physiological action of, 179.
Quercetin, 327.
Quillaia, 330.
Quillaiac acid, 330.
Quinaldine, 273.
p-Quinanisol, 274.
Quinaphenin, 280.
Quinaphthol, 280.
Quinazoline derivatives, 240.
Quinidine, 278.
Quinine, action of vinyl radical, 277, 278.
Quinine and **cinchonine,** 276.
Quinine-hydrochloro-carbamide, 280.
Quinine, insoluble derivatives of, 279; 'Loipon-Anteil,' 277; soluble derivatives of, 280; substitutes, 279.
Quinoline, action of oxidizing agents on, 239: action of reducing agents on, 239; alkaloids, 271; antiseptics, 164, 165; comparison with quinine, 272; homologues, 273; 1-hydroxy-tetra-hydro-, 48; *iso*-quinoline, pyridine, comparison of, 272; methyl-, oxidation of in body, 76; 1-oxy-2-iodo-4-chlor, 165; 1-oxy-2-iodo-4-sulphonic acid, 164; physiological action, 272; reduced derivatives, 272; synthesis of, 238; tetrahydro-*n*-ethyl-, 274; tetrahydro-*n*-methyl, 274.
iso-Quinoline-alkaloids, 284; classification, 289; nucleus, opium alkaloids, 299.
Quinopyrine, 280.
Quitenine, 278.

Racemic acid, 6; Pasteur's investigations on, 6.
Reduction, influence on sense of smell, 346; processes taking place in body, 79.
Resacetophenone, 58.
Resorcinol, 131, 140.
Resorcin, thio-, 168.

Rhamnetin, 327.
Rhamnose, methyl-, taste of, 333.
Rhodin, methyl-, 158.
Roaf and Moore, anaesthetic substances, 85.
Rosaniline, **354**.
— its derivatives, 347.

Saccharin, 336.
— derivatives, 336, 337.
Safrol, 345.
— toxic properties of, 50; iso-, 50.
Salacetol, 154.
Salen, 155.
Salicin, 322.
Salicyl-acetyl-*p*-amidophenol ether, 157.
Salicylanilide, 182.
Salicyl-phenetidin, 190, **194**.
Salicyl radical, 120.
Salicylic acid, 120, 150, 152.
— — acetol ester of, 154; acetyl derivative, 158; classification of derivatives, 153; derivatives, 151; derivatives based on salol principle, 156; derivatives, taste of, 337; dissociation of, 16; glycerin ester, 154; methoxy-methyl ester of, 154; preparation of, 151; reduction of, to pimelic acid, 31; salts of antipyrine, 205.
Saliphenin, 190.
Salipyrine, 205.
Salocoll, 193.
Salol, 155.
Salol group, 156, 157.
— principle, 55, 152; derivatives synthesized on, 156.
— substances of type of, 156.
Salophen, 157, 190.
Saloquinine, 280.
'Sapiphore' groups of Sternberg, 335.
Saponaretin, 327.
Saponarin, 327.
Saponification, 55.
Saponins, 330.
Sapotoxines, 330.
Sarsa-saponin, 330.
Saturated and unsaturated derivatives, 26.
Scammonin, 322.
Schmiedeberg, classification of narcotics, &c., 20; relation of therapeutics to pharmacology, 14.
Scoparin, 327.
Secondary amines, 171.
Senegin, 330.
Senses of taste and smell, 331.
Sesame oil, iodine preparation of, 167.
Sinalbin, 321.
Sinapin, 321.
Sinigrin, 321.
Sirolin, 146.
Smilax-saponin, 330.
Snake venoms, action of eosin on, 355.
Solubility and volatility in relation to physiological action, 14, 15, 46.
Somnal, 110.
Somnoform, 96.
Sozoiodol, preparations, 164, 165.
Sozoiodolic acid, 165.
Stereochemical influences on sense of taste, 338.
— relationships and physiological action, 53.
Stereo-isomerism, 5.
Sternberg on taste, 333.
Stilbazoline, 255.
Stibonium bases, physiological action, 54.
Stockman, physiological action of quinoline derivatives, 273.
Stomach, action of hydrochloric acid in, 55; presence of sulphocyanic acid in, 65.
Stovaine, 314.
Strophanthin, 326.
Structural formulae, 3; determination of, 3.
Strychnidine, 282.
Strychnine, 281, **283**.
Stypticin, 287.
Styptol, 287.
Styracol, 150.
Styrolene, 324.
Substituted ureas, preparation of, 215.
Substituting poisons, 17.
Succinic acid, 119.
Succinic and oxalic acids, synthesis from ethylene, 39.
Sucramine, 337.
Sucrol, 340.
Sudan 1, 352.
Sulphaminol, 168.
Sulphocyanides, formation of in body, 65.
Sulphonal, 115, 116.
Sulphonals, preparation of, 114.
Sulphones and sulphonals, distribution co-efficient of, 84.
Sulphonic acid group, influence on physiological action, 103; protection against oxidation in organism, 72.
Sulphonic esters, formation in the body with :—Gallacetophenone, 58; gentisinic acid, 57; homogentisinic acid, 57; hydroquinone, 57; paeonol, 58; phenol, 57; vanillic acid, 58; *iso*-vanillic acid, 58; veratric acid, 59.
Sulphosote, 146.
Sulphur, antiseptics containing, 186; derivatives, 126; derivatives of urea, 218.

Sulphuric acid, synthesis in body, 56.
Sulphuric and sulphurous acids, esters of, 102.
Sulphuric ester of morphia, 103.
Symmetry, influence on taste, 339.
Sympherol, 229.
Synthetic antipyretics, 171.
Synthetic processes in body, 56.

Tannal, 160.
Tannalbin, 160.
Tannate of aluminium, 160.
Tannic acid, 159; acetyl derivatives, 159.
Tannigen, 159.
Tannocase, 160.
Tannocol, 160.
Tannoform, 160.
Tannon, 160.
Tannopin, 160.
Tar, coal-, substances present in, 30.
Tartaric acids, oxidation of isomers in organism, 53; toxicity of, 118.
Taste and smell, stimulation of senses of, 332.
Taste and periodic classification of elements, 332; dependence on chemical constitution, 331; influence of ring-formation on, 340.
— of acids and bases, 332; of alcohols, 332.
— di- and poly-saccharides, 333.
— glucosides, 333.
Taurine, formation of urea derivative in body, 64.
Tellurium, formation of tellurium dimethide in body, 66.
Tertiary amines, 171.
Tetrabrom-hydroquinone-phthalein, 137.
Tetra-iodo-pyrrol, 164.
Tetronal, 116.
Thalline, 274.
Thebaine, 298.
Theobromine, 226.
— effects of NH groups, 178.
Theobromine-salicylate, 228.
Theocine, 226.
Theophylline, 226.
— synthesis of, 223.
Theory of narcosis, Baglioni, 86.
— of Overton and Meyer on hypnosis, 83, 84.
Therapeutics, rational and empiric, 13; rational, 14; obstacles to, 14; relation to pharmacology, 14.
Thermodine, 197.
Thiazine dyes, 355.
Thiocol, 145.
Thiol, 169.
Thiophene and aniline, increased toxicity on introduction of alkyls, 46.
Thiophene, physiological action of, 45.
relation to ichthyol derivatives, 170.
Thio-resorcin, 168.
Thiosinamine, 218.
Thujon, conversion into hydrate in body, 62.
Thymol, 130, **133**.
— synthesis with glycuronic acid, 61; use in perfumery, 345.
Tiodine, 169.
Tolan, preparation of, 34.
Toluidines, comparison of toxicity, 52; toxicity of, 184.
Tolyl-hydrazine, 205.
Tolyl-nitrile, 126.
Tolylpyrine, 205.
Tolysal, 205.
Traube, views on hypnosis, 85.
Trenpel and Hinsberg on aniline derivatives, 185.
Triacetone-amine, 305.
— derivatives, 306, 307, 308.
Tri-acetyl-pyrogallol, 147.
Tribromhydrin, 98.
Tri-chlor butyrate of sodium, 122.
Tri-ethyl carbinol, physiological action of, 92.
Trigemin, 109.
Tri-methyl-carbinol, physiological action of, 92.
Trional, 116.
Tri-oxy-benzenes, 147, 148.
Triphenin, 189.
Tri-phenyl-methane dyes, 354.
Trithio aldehyde, 127.
Tropaeolin .Y., 351.
Tropine, cinnamic acid derivative, 267; derivatives, mydriatic action of, 268; lactyl-, 267; physiological nature of ring, 267.
Tropines, with central stimulating action, 267.
Tropinone, 263.
— conversion into α-cocaine, 263.
Trypan blue, 353.
Trypan dyes, Ehrlich's observations on, 353.
Trypan red, 352.
Tumenol, 169.
Tussol, 206.
Tyrosin, 123.
— ethyl ester of, 123; oxidation of, in body, 75.

Unsaturated condition of molecule, influence on smell, 346.
Unsaturated substances, physiological properties, 50.
Ural, 110.
Uralium, 110.
Urea, 125.

Urea, derivatives containing bromine, 217; derivatives, taste of, 339.
— formation of derivatives in body with:—Taurine, 64; amido-benzoic acid, 64; amido-salicylic acid, 64; ethylamine-carbonate, 64.
— preparation of, 215; quinine derivatives of, 280.
— ureides, and urethanes, 218.
Ureas substituted, physiological action of, 216; sulphur derivatives, 218; synthesis of, 1.
Ureides, classification of, 219.
Urethane, 214.
Urethane, phenyl, 183; derivatives of, 196.
Urethanes, preparation of, 218.
— urea, and ureides, 218.
Uretone, 108.
Uric acid, alkyl and oxy-alkyl derivatives, 225; dioxy derivatives, 225; synthesis, 221, 222.
Urine indican, 79.
Urisol, 108.
Uropherin, 228.
Urotropin, 108.

Valency, theory of, 1, 2; variation of, 2.
Valeronitrile, 126.
Vanillic acid, 58.
iso-Vanillic acid, 59.
Vanillin, piperonal, &c., odour of, depending on concentration, 341.
Vanillin, phenetidin, 194.
— use in perfumery, 344.
Vaselines, 26.
Velocity of reactions, 8.
Veratric acid, 59.
Veratrine, decomposition products of, 180.
Veratrol, 146.
Veronal, 220.
Vesalcine, 108.
Vinylamine, toxic properties of, 50.
Vinyl-diacetone-amine, 305.
Vioform, 165.
Volatility and solubility in relation to physiological action, 14, 15, 46.

Wintergreen oil, 153.
Witt, theory of dyes, 22.
Wurtz, synthesis of hydrocarbons, 32.

Xanthates, 127.
Xanthine, 225.
Xanthine derivatives, 225, 226.
— effect of NH groups, 178.
— mono-, di-, and tri-methyl derivatives, physiological action of, 48.
— tri- and tetra-methyl derivatives, 228.
Xanthines, methylated, action of organism on, 66.

Yohimbine, 285.

OXFORD: HORACE HART
PRINTER TO THE UNIVERSITY

Mr. Edward Arnold's List of Technical & Scientific Publications

Extract from the LIVERPOOL POST of Dec. 4, 1907:—

"During recent years Mr. Edward Arnold has placed in the hands of engineers and others interested in applied science a large number of volumes which, independently altogether of their intrinsic merits as scientific works, are very fine examples of the printers' and engravers' art, and from their appearance alone would be an ornament to any scientific student's library. Fortunately for the purchaser, the publisher has shown a wise discrimination in the technical books he has added to his list, with the result that the contents of the volumes are almost without exception as worthy of perusal and study as their appearance is attractive."

Power Gas Producers.

Their Design and Application.

By PHILIP W. ROBSON,

Of the National Gas Engine Co., Ltd.; sometime Vice-Principal of the Municipal School of Technology, Manchester.

Demy 8vo., cloth, 10s. 6d. net.

The recent enormous increase in the use of gas power is largely due to the improvements in gas producers. This book, which is written by a well-known expert, goes thoroughly into the theory, design, and application of all kinds of plants, with chapters on working and general management.

Electrical Traction.

By ERNEST WILSON, WHIT. SCH., M.I.E.E.,

Professor of Electrical Engineering in the Siemens Laboratory, King's College, London,

AND FRANCIS LYDALL, B.A., B.Sc.

Two volumes, sold separately. Demy 8vo., cloth.

Vol. I., with about 300 Illustrations and Index. 15s. net.

Vol. II., with about 170 Illustrations and Index. 15s. net.

"We are most decidedly of the opinion that both of these volumes will prove of great value to engineers, and that the last volume, in view of the present great interest in the question of single phase traction, is of the utmost importance, for in it for the first time is published a great amount of data with reference to which, hitherto, the manufacturing companies concerned have observed great secrecy."—*The Times (Engineering Supplement).*

A Text-Book of Electrical Engineering.

By DR. ADOLF THOMÄLEN.

Translated by G. W. O. HOWE, M.Sc., WHIT. SCH., A.M.I.E.E.,

Lecturer in Electrical Engineering at the Central Technical College, South Kensington.

With 454 Illustrations. Royal 8vo., cloth, 15s. net.

This translation of the "Kurze Lehrbuch der Electrotechnik" is intended to fill the gap which appears to exist between the elementary text-books and the specialized works on various branches of electrical engineering.

LONDON: EDWARD ARNOLD, 41 & 43 MADDOX STREET, W.

Alternating Currents.

A Text-Book for Students of Engineering.

By C. G. LAMB, M.A., B.Sc.,
Clare College, Cambridge; Associate Member of the Institution of Electrical Engineers; Associate of the City and Guilds of London Institute.

viii + 325 pages. With upwards of 230 Illustrations. Demy 8vo., cloth, 10s. 6d. net.

The scope of this book is intended to be such as to cover approximately the range of reading in alternating current machinery and apparatus considered by the author as desirable for a student of general engineering in his last year—as, for example, a candidate for the Mechanical Sciences Tripos at Cambridge.

Electric and Magnetic Circuits.

By ELLIS H. CRAPPER, M.I.E.E.,
Head of the Electrical Engineering Department in the University College, Sheffield.

viii + 380 pages. Demy 8vo., cloth, 10s. 6d. net.

This, the introductory volume of a treatise on Electrical Engineering, deals with the fundamental principles of Electricity and Magnetism, and explains fully all the essential relationships of Electric and Magnetic Circuits met with in continuous current working. It contains a very large number of worked examples, and several hundreds of numerical examples taken from everyday practice.

Applied Electricity.

A Text-Book of Electrical Engineering for "Second Year" Students.

By J. PALEY YORKE,
Head of the Physics and Electrical Engineering Department at the London County Council School of Engineering and Navigation, Poplar.

xii + 420 pages. Crown 8vo., cloth, 7s. 6d.

This volume is a text-book of Electrical Engineering for those who have already become acquainted with the fundamental phenomena and laws of Magnetism and Electricity.

Hydraulics.

By F. C. LEA, B.Sc., A.M.INST.C.E.,
Senior Whitworth Scholar, A.R.C.S.; Lecturer in Applied Mechanics and Engineering Design, City and Guilds of London Central Technical College, London.

With about 300 Illustrations. Demy 8vo., 18s. net.

This book is intended to supply the want felt by students and teachers alike for a text-book of Hydraulics to practically cover the syllabuses of London and other Universities, and of the Institution of Civil Engineers.

Hydraulics.

By RAYMOND BUSQUET,
Professeur à l'École Industrielle de Lyon.

AUTHORIZED ENGLISH EDITION.

Translated by A. H. PEAKE, M.A.,
Demonstrator in Mechanism and Applied Mechanics in the University of Cambridge.

viii + 312 pages. With 49 Illustrations. Demy 8vo., cloth, 7s. 6d. net.

This work is a practical text-book of Applied Hydraulics, in which complete technical theories and all useful calculations for the erection of hydraulic plant are presented.

The Balancing of Engines.

By W. E. DALBY, M.A., B.Sc., M.Inst.C.E., M.I.M.E.,
Professor of Engineering, City and Guilds of London Central Technical College.

Second Edition, Revised and Enlarged.

xii+283 pages. With upwards of 180 Illustrations.
Demy 8vo., cloth, 10s. 6d. net.

CONTENTS.

Chap.
I. The Addition and Subtraction of Vector Quantities.
II. The Balancing of Revolving Masses.
III. The Balancing of Reciprocating Masses.—Long Connecting-rods.
IV. The Balancing of Locomotives.
V. Secondary Balancing.
VI. Estimation of the Primary and Secondary Unbalanced Forces and Couples.
VII. The Vibration of the Supports.
VIII. The Motion of the Connecting-rod.
Appendix. Exercises. Index.

Valves and Valve Gear Mechanisms.

By W. E. DALBY, M.A., B.Sc., M.Inst.C.E., M.I.M.E.,
Professor of Engineering, City and Guilds of London Central Technical College.

xviii+366 pages. With upwards of 200 Illustrations.
Royal 8vo., cloth, 21s. net.

Valve gears are considered in this book from two points of view—namely, the analysis of what a given gear can do, and the design of a gear to effect a stated distribution of steam. The gears analyzed are for the most part those belonging to existing and well-known types of engines, and include, amongst others, a link motion of the Great Eastern Railway, the straight link motion of the London and North-Western Railway, the Walschaert gear of the Northern of France Railway, the Joy gear of the Lancashire and Yorkshire Railway, the Sulzer gear, the Meyer gear, etc. The needs of students and draughtsmen have been kept in view throughout.

"No such systematic and complete treatment of the subject has yet been obtainable in book form, and we doubt if it could have been much better done, or by a more competent authority. The language is exact and clear, the illustrations are admirably drawn and reproduced."—*The Times.*

The Strength and Elasticity of Structural Members.

By R. J. WOODS, M.E., M.Inst.C.E.,
Fellow and Assistant Professor of Engineering, Royal Indian Engineering College, Cooper's Hill.

Second Edition, Revised.

xii+310 pages. With 292 Illustrations. Demy 8vo., cloth, 10s. 6d. net.

"To students for the final examination of the R.I.B.A. we can strongly recommend such a practical and thorough text-book."—*British Architect.*

"This is a practical book, and, although written mainly for engineering students, may be commended as one likely to prove equally useful to those engaged in active practice."—*Mechanical Engineer.*

Calculus for Engineers.

By JOHN PERRY, M.E., D.Sc., F.R.S.,
Professor of Mechanics and Mathematics in the Royal College of Science, London; Vice-President of the Physical Society; Vice-President of the Institution of Electrical Engineers.

Eighth Impression.

viii+382 pages. With 106 Illustrations. Crown 8vo., cloth, 7s. 6d.

Mathematical Drawing.

Including the Graphic Solution of Equations.

BY G. M. MINCHIN, M.A., F.R.S.,
Professor of Applied Mathematics at the Royal Indian Engineering College, Cooper's Hill;
AND JOHN BORTHWICK DALE, M.A.,
Assistant Professor of Mathematics at King's College, London.

Crown 8vo., cloth, 7s. 6d. net.

Graphic methods in Mathematics, which have attracted so much attention within the last few years, may be said to have attained a greatly increased importance by the decision of the University of London to require a knowledge of Mathematical Drawing from all candidates for the B.Sc. Degree.

The present work is largely an attempt to systematize somewhat vague methods of solving the non-algebraic equations which so often contain the solutions of physical problems.

Five-Figure Tables of Mathematical Functions.

Comprising Tables of Logarithms, Powers of Numbers, Trigonometric, Elliptic, and other Transcendental Functions.

BY JOHN BORTHWICK DALE, M.A.,
Assistant Professor of Mathematics at King's College, London

vi+92 pages. Demy 8vo., cloth, 3s. 6d. net.

This collection of Tables has been selected for use in the examinations of the University of London.

"This is a most valuable contribution to the literature of Mathematical reference . . . . To anyone engaged in almost any form of higher physical research this compilation will be an enormous boon in the way of saving time and labour and collecting data. . . . The five-figure tables of roots and powers are, perhaps, the most useful features of the work."—*Mining Journal.*

Logarithmic and Trigonometric Tables (To Five Places of Decimals).

By JOHN BORTHWICK DALE, M.A., Assistant Professor of Mathematics at King's College, London. Demy 8vo., cloth, 2s. net.

Traverse Tables.

With an Introductory Chapter on Co-ordinate Surveying.

BY HENRY LOUIS, M.A., AND G. W. CAUNT, M.A.,
Professor of Mining and Lecturer on Surveying, Armstrong College, Newcastle-on-Tyne. Lecturer in Mathematics,

xxviii+92 pages. Demy 8vo., flexible cloth, rounded corners, 4s. 6d. net.

"The admirable, compact, and inexpensive tables compiled by Professor Henry Louis and Mr. G. W. Caunt. They are just what is required by the mining student and by the practical mine surveyor. . . . Their publication at a low price renders this convenient and rapid method of working out traverse surveys accessible to a class of workers from whom it has hitherto been debarred."—*Mining Journal.*

Organic Chemistry for Advanced Students.

By JULIUS B. COHEN, PH.D., B.Sc.,

Professor of Organic Chemistry in the University of Leeds, and Associate of Owens College, Manchester.

Demy 8vo., cloth, 21s. net.

The book is written for students who have already completed an elementary course of Organic Chemistry, and is intended largely to take the place of the advanced text-book. For it has long been the opinion of the author that, when the principles of classification and synthesis and the properties of fundamental groups have been acquired, the object of the teacher should be, not to multiply facts of a similar kind, but rather to present to the student a broad and general outline of the more important branches of the subject. This method of treatment, whilst it avoids the dictionary arrangement which the text-book requires, leaves the writer the free disposal of his materials, so that he can bring together related substances, irrespective of their nature, and deal thoroughly with important theoretical questions which are often inadequately treated in the text-book.

The Chemical Synthesis of Vital Products and the Inter-relations between Organic Compounds.

By RAPHAEL MELDOLA, F.R.S., V.P.C.S., F.I.C., etc.,

Professor of Chemistry in the City and Guilds of London Technical College, Finsbury.

Vol. I., xvi+338 pages. Super Royal 8vo., cloth, 21s. net.

The great achievements of modern Organic Chemistry in the domain of the synthesis or artificial production of compounds which are known to be formed as the result of the vital activities of plants and animals have not of late years been systematically recorded. The object of the present book is to set forth a statement, as complete as possible, of the existing state of knowledge in this most important branch of science.

The Chemistry of the Diazo-Compounds.

By JOHN CANNELL CAIN, D.Sc. (Manchester and Tübingen),

Editor of the Publications of the Chemical Society.

Demy 8vo. 10s. 6d. net.

Lectures on Theoretical and Physical Chemistry.

By DR. J. H. VAN 'T HOFF,

Professor of Chemistry at the University of Berlin.

Translated by R. A. LEHFELDT, D.Sc.,

Professor of Physics at the Transvaal Technical Institute, Johannesburg.

In three volumes, demy 8vo., cloth, 28s. net, or separately as follows:

PART I. CHEMICAL DYNAMICS. 254 pages. 12s. net.
PART II. CHEMICAL STATICS. 156 pages. 8s. 6d. net.
PART III. RELATIONS BETWEEN PROPERTIES AND COMPOSITION. 143 pages, 7s. 6d. net.

Experimental Researches with the Electric Furnace.

BY HENRI MOISSAN,
Membre de l'Institut; Professor of Chemistry at the Sorbonne.

AUTHORIZED ENGLISH EDITION.

Translated by A. T. de MOUILPIED, M.Sc., Ph.D.,
Assistant Lecturer in Chemistry in the University of Liverpool.

xii + 307 pages, with Illustrations. Demy 8vo., cloth, 10s. 6d. net.

"There is hardly a page of it which is not crowded with interest, and hardly a section which does not teem with suggestion; and if the coming of this English edition of the book has been so long delayed, we may still be thankful that it has come at last, and come in a form which it is a pleasure to handle and a delight to read."—*Electrical Review.*

Electrolytic Preparations.

Exercises for use in the Laboratory by Chemists and Electro-Chemists.

BY DR. KARL ELBS,
Professor of Organic and Physical Chemistry at the University of Giessen.

Translated by R. S. HUTTON, M.Sc.,
Demonstrator and Lecturer on Electro-Chemistry at the University of Manchester.

xii + 100 pages. Demy 8vo., cloth, 4s. 6d. net.

The book contains a complete course of examples on the application of electrolysis to the preparation of both inorganic and organic substances. It will be found useful as filling a distinct gap in the text-book literature suitable for use in chemical laboratories, and should enable the chemist to make use of the many valuable and elegant methods of preparation which have been worked out during recent years, the advantages and ease of application of which he cannot appreciate without such a guide.

Introduction to Metallurgical Chemistry for Technical Students.

BY J. H. STANSBIE, B.SC. (LOND.), F.I.C.,
Associate of Mason University College, and Lecturer in the Birmingham University Technical School.

SECOND EDITION.

xii + 252 pages. Crown 8vo., cloth, 4s. 6d.

An Experimental Course of Chemistry for Agricultural Students. By T. S. DYMOND, F.I.C., Lately Principal Lecturer in the Agricultural Department, County Technical Laboratories, Chelmsford. New Impression. 192 pages, with 50 Illustrations. Crown 8vo., cloth, 2s. 6d.

A History of Chemistry.

BY DR. HUGO BAUER,
Royal Technical Institute, Stuttgart.

Translated by R. V. STANFORD, B.Sc. (LOND.),
Priestley Research Scholar in the University of Birmingham.

Crown 8vo., cloth, 3s. 6d. net.

The Becquerel Rays and the Properties of Radium.

BY THE HON. R. J. STRUTT, F.R.S.,
Fellow of Trinity College, Cambridge.

SECOND EDITION, REVISED AND ENLARGED.

viii + 222 pages, with Diagrams. Demy 8vo., cloth, 8s. 6d. net.

"If only a few more books of this type were written, there might be some hope of a general appreciation of the methods, aims, and results of science, which would go far to promote its study. . . . A book for which no praise can be excessive." *Athenæum.*

Astronomical Discovery.

BY HERBERT HALL TURNER, D.Sc., F.R.S.,
Savilian Professor of Astronomy in the University of Oxford.

xii + 225 pages, with Plates and Diagrams. Demy 8vo., cloth, 10s. 6d. net.

An Introduction to the Theory of Optics.

BY ARTHUR SCHUSTER, Ph.D., Sc.D., F.R.S.,
Recently Professor of Physics at the University of Manchester.

xvi + 340 pages, with Illustrations. Demy 8vo., cloth, 15s. net.

"We know of no book written with a set purpose better adapted to serve the purpose for which it was written, nor any that the earnest student of optics will find more interesting and profitable. The work itself, without the confession of the preface, shows that Professor Schuster is a teacher, and every page bears evidence that he is a master of his subject . . . We heartily recommend the book to our readers."—*Ophthalmic Review.*

Wood.

A Manual of the Natural History and Industrial Applications of the Timbers of Commerce.

BY G. S. BOULGER, F.L.S., F.G.S., A.S.I.,
Professor of Botany and Lecturer on Forestry in the City of London College, and formerly in the Royal Agricultural College.

NEW EDITION. Revised and Enlarged and profusely illustrated.
Demy 8vo., 12s. 6d. net.

"It is just the book that has long been wanted by land agents, foresters, and woodmen, and it should find a place in all technical school libraries."—*Field.*

Manual of Alcoholic Fermentation and the Allied Industries.

BY CHARLES G. MATTHEWS, F.I.C., F.C.S., ETC.

xvi + 295 pages, with 8 Plates, and 40 Illustrations. Crown 8vo., cloth, 7s. 6d. net.

"This is a book worthy of its author, and well worth perusing by every student. . . . The student, both old and young, as well as the practical brewer, will find this book gives him some very useful information."—*Brewers' Guardian.*

The Evolution Theory. By DR. AUGUST WEISMANN, Professor of Zoology in the University of Freiburg in Breisgau. Translated, with the Author's co-operation, by J. ARTHUR THOMSON, Regius Professor of Natural History in the University of Aberdeen; and MARGARET THOMSON. Two vols., xvi + 416 and viii + 396 pages, with over 130 Illustrations. Royal 8vo., cloth, 32s. net.

"The subject has never been so fully and comprehensively expounded before; and it is not necessary to subscribe to all the author's tenets in order to recognise the value and the absorbing interest of his exposition, with its prodigious wealth of illustration, its vast store of zoological knowledge, its ingenious interpretations and far-reaching theories. English readers have reason to be grateful to Professor and Mrs. Thomson for their admirable translation."—*The Times.*

The Chances of Death and Other Studies in Evolution. By KARL PEARSON, M.A., F.R.S., Professor of Applied Mathematics in University College, London, and formerly Fellow of King's College, Cambridge. 2 vols., xii + 388 and 460 pages, with numerous Illustrations. Demy 8vo., cloth, 25s. net.

The Life of the Salmon. With reference more especially to the Fish in Scotland. By W. L. CALDERWOOD, F.R.S.E., Inspector of Salmon Fisheries for Scotland. Illustrated. Demy 8vo., 7s. 6d. net.

"We have no hesitation whatever in advising all persons interested in the salmon, whether as fishermen, naturalists, or legislators, to add this book to their libraries."—*Nature.*

Animal Behaviour. By Professor C. LLOYD MORGAN, LL.D., F.R.S., Principal of University College, Bristol. viii + 344 pages, with 26 Illustrations. Large crown 8vo., cloth, 10s. 6d.

This important contribution to the fascinating subject of animal psychology covers the whole ground from the behaviour of cells up to that of the most highly developed animals.

BY THE SAME AUTHOR.

Habit and Instinct. viii + 352 pages, with Photogravure Frontispiece. Demy 8vo., cloth, 16s.

Professor ALFRED RUSSEL WALLACE:—"An admirable introduction to the study of a most important and fascinating branch of biology, now for the first time based upon a substantial foundation of carefully observed facts and logical induction from them."

BY THE SAME AUTHOR.

The Springs of Conduct. Cheaper Edition. viii + 317 pages. Large crown 8vo., cloth, 3s. 6d. This volume deals with the Source and Limits of Knowledge, the Study of Nature, the Evolution of Scientific Knowledge, Body, and Mind, Choice, Feeling, and Conduct.

BY THE SAME AUTHOR.

Psychology for Teachers. New Edition, entirely rewritten. xii + 308 pages. Crown 8vo., cloth, 4s. 6d.

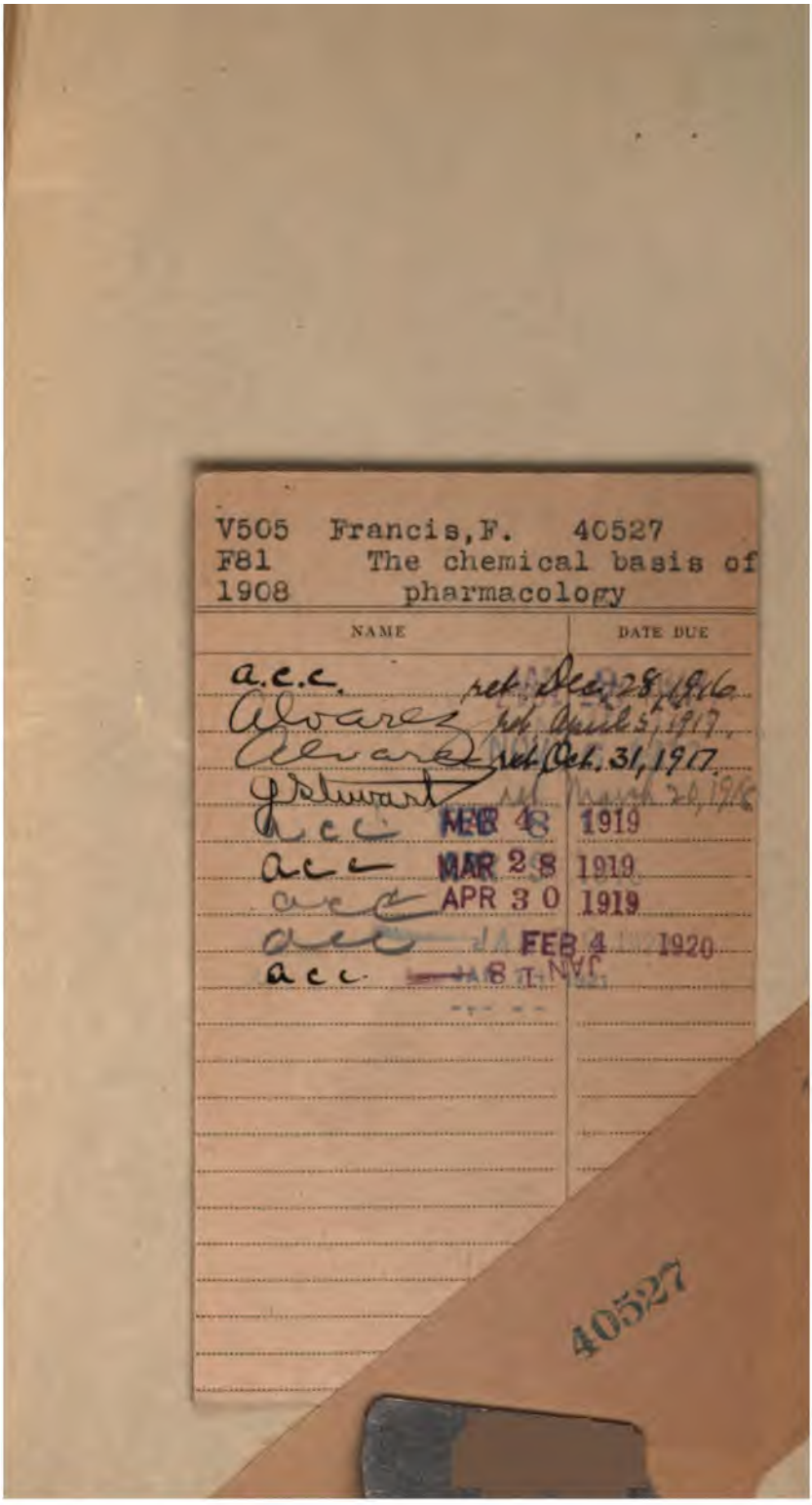
An Introduction to Child Study. By Dr. W. B. DRUMMOND. Crown 8vo., cloth, 6s. net.

The Child's Mind: Its Growth and Training. By W. E. URWICK, University of Leeds. Crown 8vo., cloth, 4s. 6d. net.

LANE MEDICAL LIBRARY

To avoid fine, this book should be returned on or before the date last stamped below.

JAN 9 1917
JAN 27 1917
NOV 6 1917
MAR 26 1918
FEB 8 1919
JAN 30 1920



V505 Francis, F. 40527
F81 The chemical basis of
1908 pharmacology

NAME	DATE DUE
a.c.c.	ret. Dec. 28, 1916
Alvarez	ret. April 5, 1917
Alvarez	ret. Oct. 31, 1917
J Stewart	ret. March 21, 1916
acc	FEB 4 8 1919
acc	MAR 2 8 1919
acc	APR 3 0 1919
acc	FEB 4 1920
acc	MAR 8 1920

40527